FORMULATION DEVELOPMENT AND EVALUATION OF ETORICOXIB ORAL DISINTEGRATION TABLET BY USING ION EXCHANGE RESIN COMPLEXATION TECHNIQUE

Dissertation submitted to

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In partial fulfillment of the requirements for the award of the degree of

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IN

PHARMACEUTICS

Submitted By

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CERTIFICATE

This is to certify that the investigation described in the dissertation entitled **"Formulation development and evaluation of etoricoxib oral disintegration tablet by using ion exchange resin complexation technique"** submitted by Reg.No:261510405 was carried out in the Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, AnandNagar,Krishnankoil-626 126, which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the supervision and guidance of **Dr.S.R.SENTHILKUMAR,M.Pharm.Ph.D.,** Department of Pharmaceutics for the partial fulfillment of degree of MASTER OF PHARMACY in PHARMACEUTICS.

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EVALUATION CERTIFICATE

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1.EXAMINER **2. EXAMINER**

Date:

Centre: Arulmigu Kalasalingam College of Pharmacy
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"Talent and capabilities are of course necessary but opportunities and right guidance is two very important backups without which anyone can climb the ladder to success".

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Who always stand behind me as shadow and their moral support, faith wisdom and strength have inspired me to be the best I can be.

INDEX

S no.	Abbreviation	Full form
1	ODTs	Orally Disintegrating Tablets
2	CDER	Center for Drug Evaluation and Research
3	GIT	gastrointestinal tract
4	FDTs	Fast dissolving tablet
5	FDA's	Food and Drug Administration's
6	WHO	World health organization
7	MDTs	Mouth dissolving tablets
8	WOW	without water’
9	NDDSs	novel drug-delivery systems
10	COX-1	Cyclo oxygenase enzyme -1
11	COX-2	Cyclo oxygenase enzyme -2
12	HPC	Hydrox propyl cellulose
13	HPMC	Hydroxyl propyl methyl cellulose
14	NSAIDs	Non steroid anti-inflammatory drugs
15	CYP 450	cytochrome P450
16	EXB	Etoricoxib
17	AUC	Area under curve
18	FTIR	Fourier transform infrared spectroscopy

19	DSC	differential scanning calorimeter
20	UV	Ultra violet
21	AA	arachidonic acid
22	TxA	Thromboxane
23	PG	prostaglandin
24	FAP	familial adenomatous polyposis
25	LOD	Loss on drying
26	mm	Mille meter
27	μm	Micro metre
28	DRC	Drug resin complex
29	EDI	Etoricoxib dispersion improvement
30	ETI	Etoricoxib taste improvement
31	RH	Room humidity
32	RT	Room temperature

INTRODUCTION

Over the past three decades, orally disintegrating tablets (ODTs) have gained much attention as a preferred alternative to conventional oral dosage forms such as tablets and capsules. An ODT is a solid dosage form that disintegrates and dissolves in the mouth (either or beneath the tongue or in the buccal cavity) without water within 60 seconds or less [1]. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines in the Orange Book an ODT as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue [2]. The European Pharmacopoeia however defines a similar term; orally disperse, as a tablet that can be placed in the mouth where it disperses rapidly before swallowing [3].

These tablets are distinguished from conventional sublingual tablets, lozenges, and buccal tablets which require more than a minute to dissolve in the mouth. In the literature, ODTs also are called orally disintegrating, orally disperse, mouth-dissolving, quick-dissolve, fast-melt, and rapid-disintegrating tablets and freeze-dried wafers [4].

Orally disintegration tablet release drug in the mouth for absorption through local oromucosal tissues and through pre-gastric (*e.g.,* oral cavity, pharynx, and esophagus), gastric (*i.e.,* stomach), and post-gastric (*e.g.,* small and large intestines) segments of the gastrointestinal tract [5]. In this article, the term conventional oral dosage forms refers to tablets and capsules that must be swallowed with water for dissolution, release, and absorption of the drug in the stomach and GIT distal sites [6].

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms [7]. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms [8].

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes [9]. Tablets and hard gelatin capsules constitute a

major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected [10].

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take it water [11]. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms [12]. Although chewable tablets have been on the market for some time, they are not the same as the new ODTs. Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth [13].

Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%) [14].

Orally disintegration tablet products have been developed for numerous indications ranging from migraines (for which rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia) [15].

A freeze-dried wafer:

Is a quick-dissolving, thin matrix that contains a medicinal agent that does not need water for swallowing. This fragile dosage form requires unit-dose packaging to ensure physical stability. The wafer disintegrates instantaneously in the oral cavity and releases drug, which dissolves or disperses in the saliva. [16] The saliva is swallowed and the drug is absorbed across the gastrointestinal tract (GIT). An orally disintegrating tablet (ODT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT1 [17].

A quick-dissolving tablet:

A quick-dissolving tablet (also known as a fast-dissolving, fast-dissolving multiparticulate, rapid-dissolving, mouth-dissolving, fast melting, or orodispersing tablets) is an oral tablet that does not require water for swallowing. The tablet dissolves within 60 seconds when placed in the mouth [18]. The active ingredients are absorbed through mucous membranes in the mouth and GIT and enter the blood stream. A fraction of pre-gastric drug absorption may bypass the digestive system and metabolism by the stomach acids and enzymes. In general, the tablets are physically robust and can be packaged in multi dose containers [1, 19].

WHO Guidelines:

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

This guidance provides pharmaceutical manufacturers of new and generic drug products with an Agency perspective on the definition of an orally disintegrating tablet (ODT)—which is a different dosage form than, for example, a chewable tablet or a tablet that should be swallowed whole with liquid—and also provides recommendations to applicants who would like to designate proposed products as ODTs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that something is suggested or recommended, but not required [20].

Ideal properties of ODTS:

The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable ODT to perform this unique function [21].

An ideal ODT should meet the following criteria:

- Does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds
- Has sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling
- Allow high drug loading
- Has a pleasant mouth feel
- Is insensitive to environmental conditions such as humidity and temperature
- Is adaptable and amenable to existing processing and packaging machineries
- Is cost-effective [22].

The Need for Development of ODTS:

The need for non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

Challenge in formulating ODTS:

Palatability:

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance [23].

Mechanical strength:

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multi dose bottles, such as Wowtab® by Yamanou [24].

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging [25].

Amount of drug:

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Aqueous solubility:

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite [26].

Size of tablet:

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve [27].

Selection of ODT Drug Candidates:

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms. In general, an ODT is formulated as a bioequivalent line extension of an existing oral dosage form. Under this circumstance, it is assumed that the absorption of a drug molecule from the ODT occurs in the post-gastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case. For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form [28].

It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both. If significantly higher plasma levels have been observed, pre-gastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT. For example, safety profiles may be improved for drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT [29].

Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2) and those able to permeate oral mucosal tissue are considered ideal for ODT formulations. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.

Similarly, patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations. Drugs with a short half-life and frequent dosing, drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved or those which require controlled or sustained release are unsuitable candidates of rapidly dissolving oral dosage forms.

Researchers have formulated ODT for various categories of drugs used for therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, antiallergic, anti-

epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction [30].

Approaches to ODT development:

The fast disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to develop rapidly dissolving oral dosage forms include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipents in the formulation. As is often the case, a technology that is originally developed to address a particular administration need can quickly become adopted as part of a pharmaceutical company's product life cycle management strategy, which is precisely what has happened with ODT technologies. The technologies that have been used by various researchers to prepare orally disintegrating dosage forms include: Freeze Drying or Lyophilization, Molding, Direct Compression, Disintegrant addition, Sublimation, Spray Drying, Mass Extrusion, Cotton-candy process, Nano Crystal TM Technology, Oral films/wafers. Specific properties of the various ODT technologies are listed [31, 32].

Types of dosage forms:

Dosage forms are the means (or the forms) by which drug molecules is delivery to site of actions within the body. The need for dosage forms:

- Accurate dose.
- Protections. E.g. coated tablet, sealed ampoules.
- Protections of gastric juice.
- Masking taste and odor.
- Placement of drug within body tissues.
- Sustained release medications.
- Controlled release medications.
- Optimal drug action
- Insertion of drug in to body cavities.
- Use of desired vehicle for insoluble drugs.

Route of administration:

A route of administration in pharmacology in toxicology is the path by which a drug, fluid, poison, or other substance is taken in to the body. Route of administration are generally classified by the location which the substance is applied. Common examples include oral and intravenous administration.

Type of administrations:

- Oral route .many drugs of administered orally as liquids, capsules, tablets,
- Parenteral route.
- Inhalation.
- Topical

Tablet:

Tablet may be defined as the solid unit dosage form of medicament or medicaments with or without suitable excipients and prepared either molding or by compression. It comprises a mixture of active substance and excipients, usually in powder form, pressed or compacted form a powder in to a solid dose.

Types of tablets:

(A) Tablet ingested orally:

- Compressed tablet e.g. paracetamol tablet
- Multiple compressed tablet
- Repeat action tablet
- Delayed release tablet e.g. enteric coated tablet
- Sugar coated tablet e.g. multivitamin tablet.
- Film coated tablet e.g. Metronidazole
- Orally disintegrating tablet e.g. ondonsetron
- Chewable tablet e.g. antacid tablet

(B) Tablet used in buccal cavity:

- Buccal tablet e.g. vitamin-c tablet
- Sublingual tablet e.g. nitro glycerin
- Troches or lozenges
- Dental cone

(C) Tablet administered by other route:

- Implantation tablet
- Vaginal tablet

(D) Tablet used to prepare solution:

- Effervescent tablet e.g. dispirin tablet (aspirin)
- Dispensing tablet e.g. enzyme tablet
- Hypodermic tablet (digiplex) ([33].

Orally disintegrating tablet

Orally disintegrating tablets (ODTs) were defined as a solid dosage form containing medicinal substances that disintegrate within a matter of seconds when placed on tongue. According to European Pharmacopeia, ODTs were defined as orodisperse that can be placed in mouth where it disperses rapidly before swallowing. These are appropriate dosage form for older people, children, and bedridden patients because it can be difficult for these patients to swallow conventional tablets or capsules. In these patients, medication compliance and therapeutic effect could be improved by taking ODTs that can rapidly and easily disintegrate in oral cavity[34].

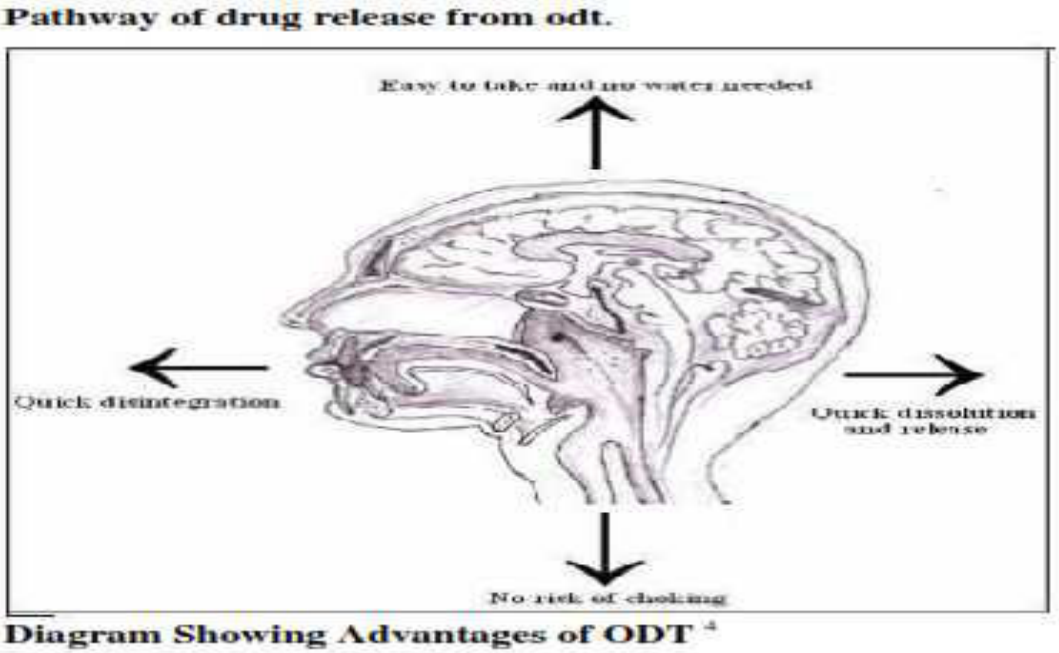

Figure no. 1 orally disintegration tablet

Advantages of ODT:

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric, mentally ill, disabled and uncooperative patients.
- Rapid dissolution of drug and absorption may produce rapid onset of action.
- Pregastric absorption can result in improved bioavailability, and as a result of reduced dosage, improved clinical performance by reducing side effects.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
- Convenience of administration and accurate dose as compared to liquids.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increases.
- Good mouth feel property of ODTS helps to change the psychology of medication as "bitter pill" particularly in pediatrics' patients.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- New business opportunities product differentiation, line extension and lifecycle management, exclusivity of the product promotion and patent-life extension.

Disadvantages of ODT:

- Rapid disintegrating tablets are hygroscopic in nature so must be kept at controlled environment i.e. Humidity and temperature.
- For properly stabilization and safety of stable product, ODT requires special packaging.
- Usually have insufficient mechanical strength. Hence, careful handling is required.
- Leave unpleasant taste and/or grittiness in mouth if not formulated properly [35].

Need for ODTs:

- Orally disintegrating dosage forms are particularly suitable for patients find it inconvenient to swallow traditional tablets and capsules with glass of water.
- Pediatric and geriatric patients
- Patients who are unwilling to take solid preparation due to fear of choking
- A patient with persistent nausea, who may be in journey, or has little or no access to water
- Increased bioavailability and faster onset of action are a major claim of these formulations [36].

Figure no. 2 Breakdown of ODT

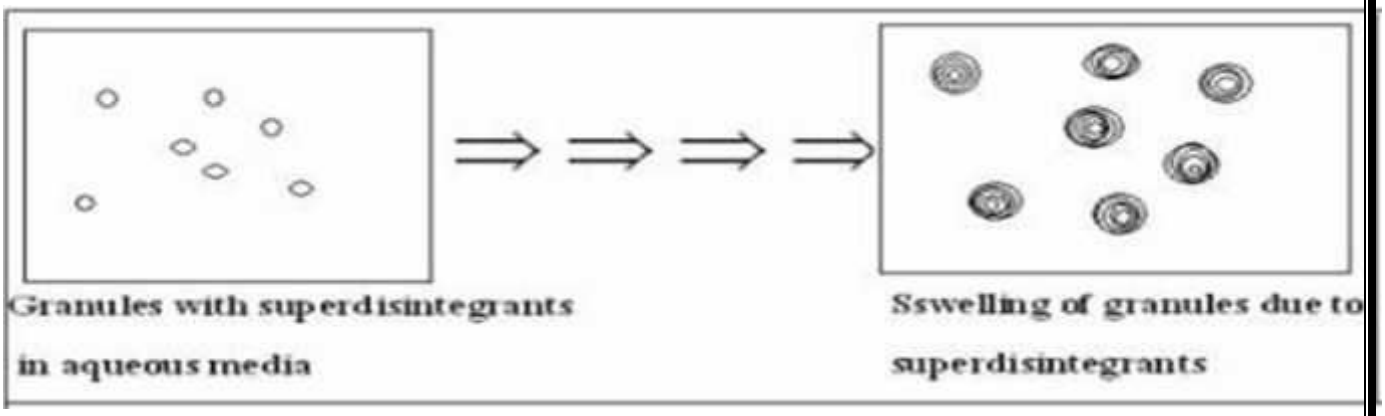

Figure no. 3 Mechanism of drug release

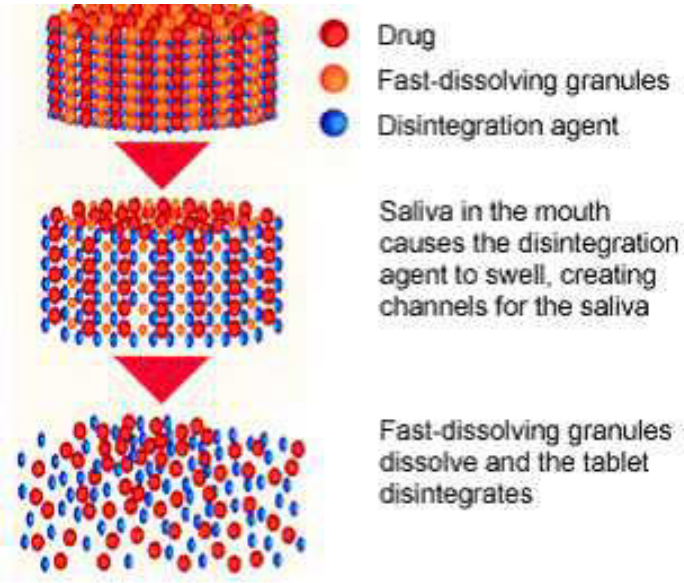

Figure no. 4 Disintegration of drug particles

Main ingredients used in preparation of ODT:

Important ingredients that are used in the formulation of ODT should allow quick release of the drug, resulting in faster dissolution. This includes both the active and the excipients. Disintegration and solubilization of a directly compressed tablet depend on single or combined effects of disintegrate, water soluble excipients and effervescent agents [37].

Regulatory definitions:

US Definition:

- Orally disintegrating tablet
- A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue
- Tablet weight <500mg. In-vitro USP disintegration test <30 seconds.
- FDA guidance for industry -orally disintegrating tablets

EU Definition:

- Orodispersible tablets
- Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed
- Disintegration Test: Orodispersible tablets disintegrate within 3 mins when examined by the test for disintegration.
- European Pharmacopoeia [38].

Figure no. 5 Disintegration of ODT

Mechanism of tablet disintegration:

- Swelling
- Porosity and Capillary action
- Deformation
- Due to disintegrating particle/particle repulsive forces

Swelling:

Although not all effective disintegrant swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

Porosity and Capillary Action (Wicking):

Effective disintegrant that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the inter-particulate bonds causing the tablet to break apart.

Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking. In recent years, several newer agents have been developed known as "Super disintegrants". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the super disintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective super disintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing

high-dose drugs. Super disintegrants offer significant improvements over starch. But hygroscopicity may be a problem in some formulations. As day's passes, demand for faster disintegrating formulation is increased. Super disintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective Intra granularly. And this super disintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration. Three major groups of compounds have been developed which swell to many times their original size when placed in water while producing minimal viscosity effects [39].

Selection of super-disintegrates:

The ideal superdisintegrant should have:

- Poor gel formation.
- Good hydration capacity.
- Good molding and flow properties
- No tendency to form complexes with the drugs.
- Good mouth feel.
- It should also be compatible with the other excipients and have desirable tableting properties [40].

Mechanism action of super-disintegrant:

Swelling:

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down [41].

Figure no. 6 Swelling

Porosity and capillary action (Wicking):

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipients and on tableting conditions. For this type of disintegrants, maintenance of porous structure and low interfacial tension toward aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles [42].

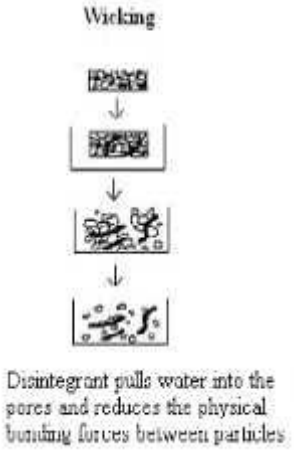

Figure no.7 Wicking

Due to disintegrating particle-particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that no swelling particles also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. [43].

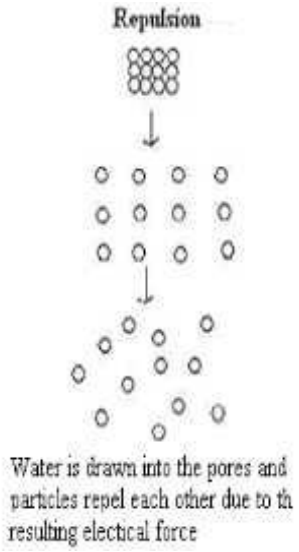

Figure no. 8 Particle-particle repulsive forces

Due to deformation:

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet [44].

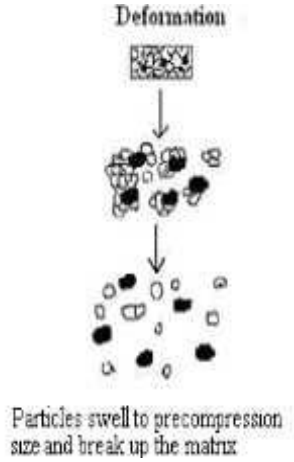

Figure no.9 Deformation

Because of heat of wetting (air expansion):

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents [45].

Due to release of gases:

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two fraction of formulation [46].

By enzymatic reaction:

Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration [47].

Table1.1 List of superdisintegrants:

S NO.	Example	Superdisintegrants	Mechanism of action	Special comments
1	Crosslinked cellulose	Crosscarmellose Ac-Di-Sol Primellose Vivasol	Swells 4-8 folds in <10seconds. Swelling and wicking both	Swelling is in two dimensions. -Direct compression or granulation -Starch free
2	Crosslinked PVP	Crosspovidone	Swells 7-12 folds in <30 second	Swells in three dimensions and high level serve as sustain release matrix
3	Crosslinked starch	Sodium starch Glycolate	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level serve as sustain release matrix
4	Cross linked alginic acid	Alginic acid NF	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
5	Natural super Disintegrates	Soya Polysaccharides	Rapid Dissolving	Does not contain any starch or sugar. Used in nutritional products[48].

Table no. 2 Synthetic superdisintegrant

S.NO.	**Synthetic superdisintegrant**	**Properties**	**Effective concentration for Disintegrants**
1	Crospovidone	1. It is completely insoluble in water. Rapidly disperses and swells in water. Greatest rate of swelling .compared to other disintegrants 2. Available in grades if needed for improving state of dispersion in the powder blend 3. Swelling index - 58±1.5% *v/v*	It is used in the range of 1-3% *w/w*
2	Croscarmellose sodium	1.It is insoluble in water, although it rapidly swells to 4-8 times its original volume on contact with water 2. Specific surface area - 0.81-0.83m/g 3. Swelling index- 65±1.7% *v/v*	It may be used as a tablet disintegrant at concentration up to5% *w/w*, although normally 2% *w/w* is used in tablets prepared by direct compression and 3% *w/w*in tablets prepared by wet-granulation process
3	Sodium starch glycolate	1. Absorbs water rapidly, resulting in swelling up to 6%. High concentration causes gelling and loss of disintegration 2.Swelling index - 52±1.2% *v/v*	It is used in the range of 4-6%. Above 8%, disintegration times may actually increase due to gelling and its subsequent viscosity producing effects
4	Polacrilin potassium	No lump formation after disintegration High compatibility with excipients and common therapeutic	Used as a tablet disintegrant and as taste masking agent for various drugs [49].

Taste-masking agents:

Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation. The approaches are as follows:

- Layering the drug onto inert beads using a binder followed by coating with a taste-masking polymer.
- Granulating the drug and coating with a taste masking polymer.
- Spray drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles.
- Complexation by the use of inclusion in cyclodextrins.
- Psychological modulation of bitterness
- Coacervation to form microencapsulated drug within a polymer.
- Formation of pellets by extrusion spheronization [50].

Sweeteners:

Sucrose and other natural sweeteners, such as sorbitol, can be used in effervescent products, although artificial sweetening agents are customary. However, the application of artificial sweeteners is restricted by health regulations. Saccharin or its sodium and calcium salts are used as sweeteners. Aspartame is also employed as a sweetener in effervescent tablets. Earlier, cyclamates and cyclamic acid were the artificial sweeteners of choice, but their use has now been restricted. Some commonly used sweeteners are:

Example: Sorbitol, Mannitol, Maltitol solution, Maltitol, Xylitol, Erythritol, Sucrose, Fructose,

Maltose, aspartame, Glycerin, sugars derivatives etc [51].

Binders:

Main role of Binders is to keep the composition of these fast melting tablets together during the compression stage. Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as polyethylene glycol. The right selection of a binder or

combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–35^{o}C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system.

Example:

Binders commonly used are cellulosic polymers such as ethylcellulose, hydroxylpropyl cellulose (HPC), and hydroxyl propylmethyl cellulose (HPMC), alone or in admixtures povidones, polyvinyl alcohols, and acrylic polymers. Acrylic polymers used are the ammoniomethacrylate copolymer, polyacrylate, and polymethacrylate. Among the cellulosic [52].

Antistatic agent:

An antistatic agent is a compound used for treatment of materials or their surfaces in order to reduce or eliminate buildup of static electricity generally caused by the turboelectric effect. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling. Example: colloidal silica (Aerosil), precipitated silica (Sylod.FP244), micronized or non micronized talc, maltodextrins, beta-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearylfumarate, micronized polyoxyethylene glycol (micronized Macrogol 6000), leucine, sodium benzoate are used as lubricant [53].

Lubricants:

Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

Example: Magnesium stearate, stearic acid, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin etc [54].

Flavors:

Example**:** Peppermint flavor, clove oil, anise oil, eucalyptus oil. Flavoring agents include, vanilla, citrus oils, fruit essences etc. [55].

Fillers:

Example: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide etc. [56].

Surface active agents: Example: sodiumdoecylsulfate, sodiumlaurylsulfate, Tweens, Spans, polyoxyethylene stearat [57].

Table no.3: Excipients profile details:

S no.	Flavors'	Fillers	Surface active agents	Binder	color	Lubricants	Sweeteners'
1	Peppermint Flavor	Directly compressible spray dried Mannitol	Sodium doecyl sulfate	Polyvinyl pyrrolidone (PVP)	Sunset yellow	Stearic acid	Aspartame
2	Cooling Flavor	Sorbitol	Sodium lauryl Sulfate	Hydroxy propylmethyl cellulose (HPMC)	Amaranth	Magnesium stearate	Sugars derivative
3	Flavor oils and Flavoring aromatic oil	Xylitol	Sorbitan fatty acid esters (spans)	Polyvinylalcohol (PVA)		Zinc state	
4	Peppermint Oil	Magnesium carbonate	Polyoxy ethylene stearates			Calcium stat	

5	Clove oil	Calcium Bay oil phosphate	Polyoxy ethylene sorbitan fatty acid esters(tweens)			Polyethylene glycole	
6	Bay oil	Calcium sulfate				Liquid paraffin	
7	Anise oil	Pregelatinized starch				Coilloidal silicon dioxide	
8	Oil of bitter almonds	trisilicate Magnesium				Magnesium lauryl sulfate	

Taste masking methods:

- ✓ The drugs are mostly bitter in nature. Skillful taste masking is needed to hide the bitter taste in ODT formulations. Following methods are used in Taste masking.
- ✓ Simple wet granulation method or rollercompaction of other excipients. Spray drying can also employed to shroud the drug.
- ✓ Drugs can be sifted twice or thrice in small particle size mesh with excipients such as sweeteners and flavors etc.
- ✓ Drug particles are coated directly.
- ✓ Granulation of the drug with certain excipients followed by the polymer coating.
- ✓ If the drug is tasteless or very low dose, direct blend of bulk drug substance into fast disintegrating matrix is straightforward.
- ✓ Formation of pellets by extrusion spheronization.
- ✓ Coacervation to form microencapsulated drug within a polymer.
- ✓ Cyclodextrins can be used to trap or complex, cyclodextrin help to solubilze many drugs.

- ✓ Drug complexation with resinates are insoluble and no taste in oral cavity. Examples of drugs where this technique has been successfully demonstrated include ranitidine, risperidone and paroxetine.
- ✓ Other methods include hot melt and supercritical fluids.
- ✓ Adjustment of pH Values: Many drugs are less soluble at pH different from the pH value of the mouth, which are around 5.9. Solubilization inhibitor, such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or calcium carbonate, was added to increase the pH when granules including a drug-sildenafil dissolved in aqueous medium, the bitter taste of the drug were successfully masked by a sweetener alone. [58].

Table no.4 Approaches for preparation of methods:

Technologies			
Conventional technologies		Patented technologies	
1	Freeze drying	1	Zydus technology
2	Sublimation	2	Orasolv technology
3	Spray drying	3	Durasalv technology
4	Ion exchange resin complexation	4	Wowtab technology
5	Mass extrusion	5	Flshdose technology
6	Moulding	6	Flashtab technology
7	Direct compression	7	Oraquick technology
8	Cotton candy method	8	Pharmabust technology
9	Nanotization	9	Nanocrystal technology
10	Fast dissolving flim	10	Frosta technology
11	Melt granulation	11	Dispersible technology

Freeze drying or lyophilisation:

A process, in which water is sublimated from the product after freezing, is called freeze drying. Freeze dried forms offer more rapid dissolution than other available solid products. Lyophilization can be used to prepare tablets that have very porous open matrix network into

which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of final product. These include suspending agents, wetting agents, preservatives, antioxidants, colors and flavors. The preferred drug characteristics for freeze drying formulations are water insoluble, low dose, chemically stable, small particle size and tasteless.

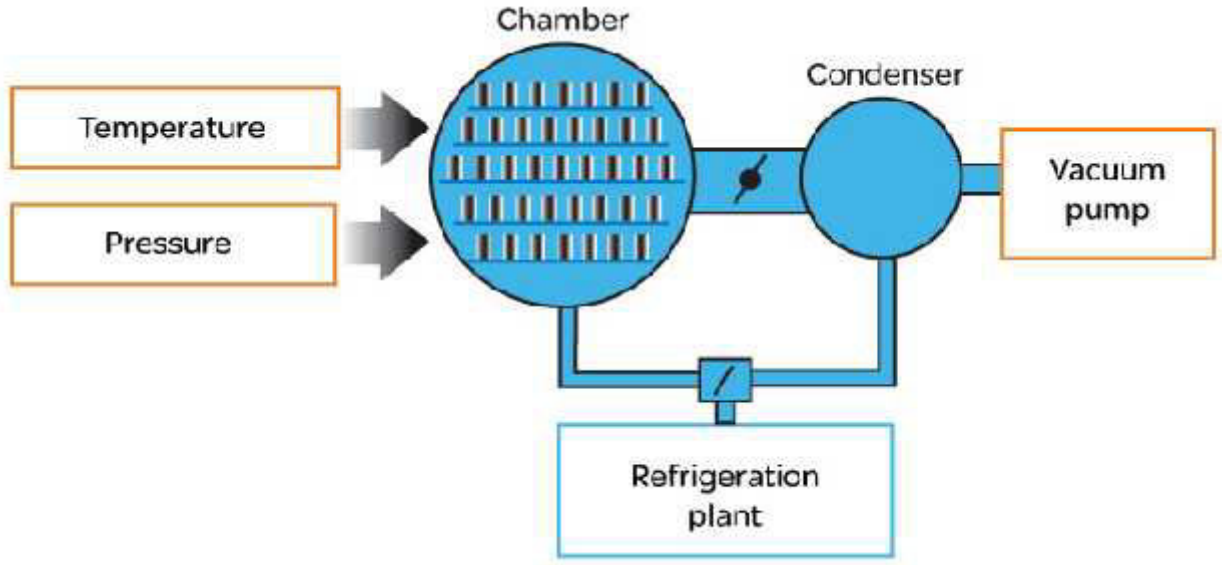

Figure no. 10 Freeze drying or lyophilisation

Merits:

Pharmaceutical substances can be processed at non elevated temperature, thereby eliminating adverse thermal effects.

Demerits:

(i) Due to high cost of equipments Lyophilization is relatively expensive and time consuming manufacturing process.

(ii) Fragility, which make the use of conventional packing difficult and poor stability during storage under stressful condition [59].

Sublimation:

This process involves addition of some inert volatile substances like urea, urethane, naphthalene, camphor, etc to other excipients and the compression of blend into tablet. Removal of volatile material by sublimation creates pores in tablet structure, due to which tablet dissolves when comes in contact with saliva. Additionally several solvents like cyclohexane, benzene etc can also be used as pore forming agents. Orodispersable Tablets with highly porous structure and good mechanical strength have been developed by this method [60].

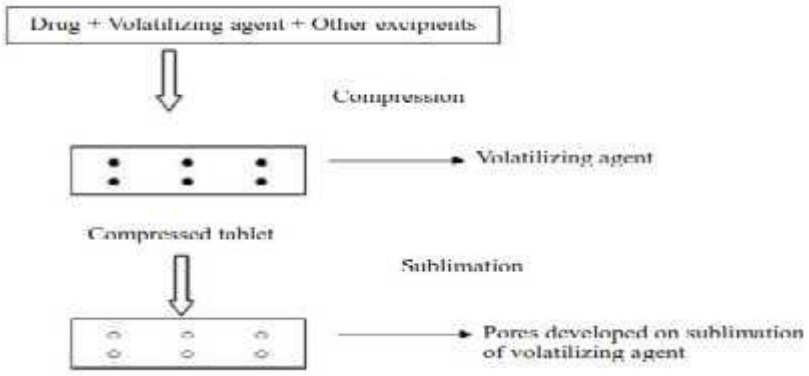

Figure no.11 Sublimation

Spray drying:

A highly porous and fine powder is prepared by spray drying an aqueous composition containing support matrix and other components. This is then mixed with active ingredient and compressed into tablet. The formulations contained hydrolyzed and unhydrolyzed gelatin as a supporting agent for the matrix, mannitol as a bulking agent and sodium starch glycolate/croscaramellose as a disintegrant. Disintegration and dissolution were further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g., sodium bicarbonate). The suspension of above excipients was spray-dried to yield a porous powder which was compressed into tablets. Tablets manufactured by this method disintegrated in < 20 sec. in an aqueous medium [61].

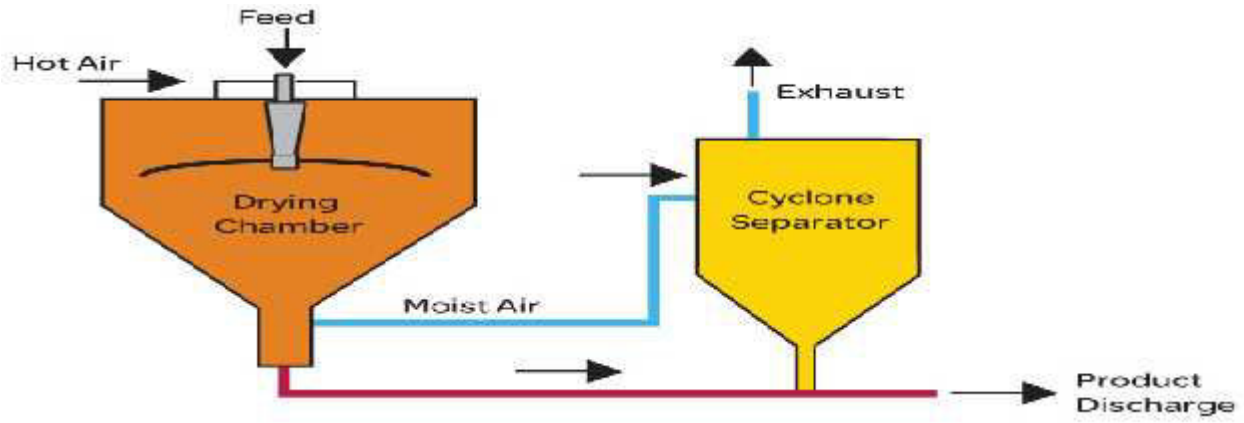

Figure no.12 spray drying

Molding:

Molded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air drying.

Figure no. 13 Molding

Figure no.14 molding tablet

Merits:

- Molded tablets posses' porous structure, which facilitates rapid disintegration and easy dissolution.
- Molded tablets offer improved taste due to water-soluble sugars present in dispersion matrix.

Demerits:

- But molded tablets lack good mechanical strength and can undergo breakage or erosion during
- Handling and opening of blister packs increase mechanical strength [62].

Heat molding:

A molten matrix in which drug is dissolved or dispersed can be directly molded into Orodispersable Tablets. [63].

No vacuum lyophilization:

This process involves evaporation of solvent from a drug solution or suspension at a standard pressure [64].

Mass extrusion:

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and there by masking their bitter taste [65].

Direct compression:

The disintegrant addition technology (direct compression) is the most preferred technique to manufacture the tablets. Advantages:

- High doses can be accommodated and final weight of the tablet can exceed that of other methods.
- Easiest way to manufacture the MDT tablets.
- Conventional equipment and commonly available excipients are used.
- A limited number of processing steps are involved. Cost-effectiveness

Tablet size and hardness strongly affect the disintegrant efficacy. Hard and large tablets have more disintegration time than normally required. Very soft and small tablets have low mechanical strength. So, an optimum kind and concentration of disintegrant should be chosen to achieve quick disintegration and high dissolution rates. Above the critical concentration level, however, disintegration time remains approximately constant or even increases [66].

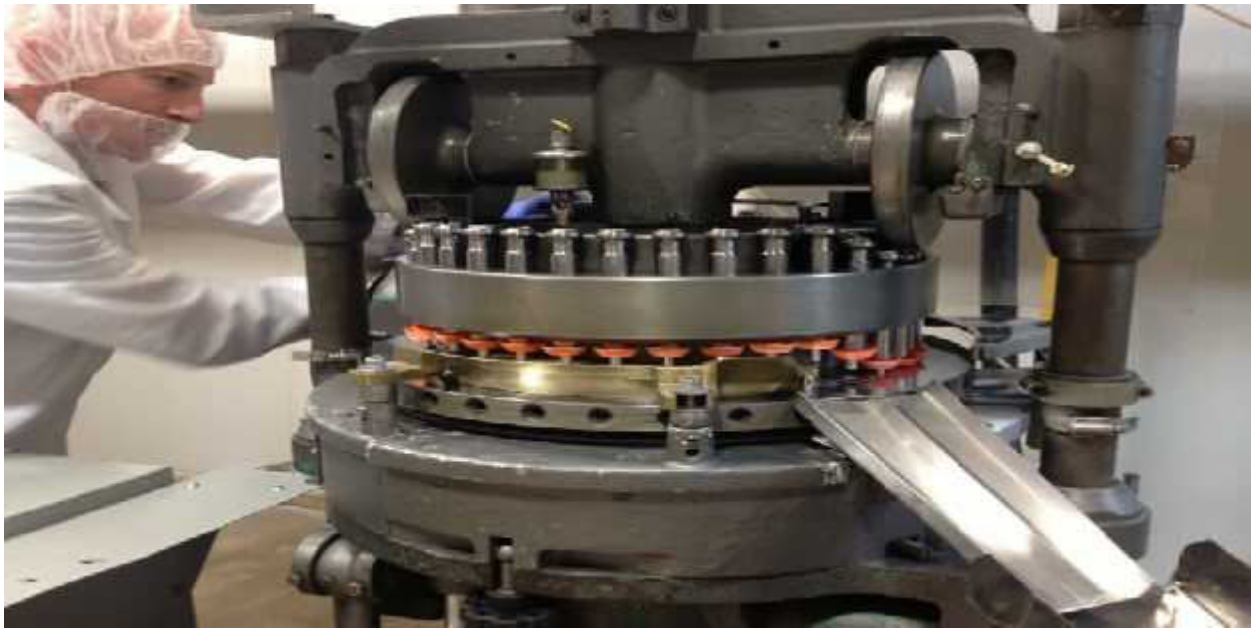

Figure no.15 direct compression

Cotton-candy process:

In this process Shear form technology is used in the preparation of a matrix known as FLOSS, made from the combination of the recipients either alone or with the drugs. The fibrous nature of the floss is similar to the cotton-candy fibers. The floss is commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180-266 °F. Other polysaccharides such aspolymaltodextrins and polydextrose can be transformed into fibers at 30-40% lower temperature range [67].

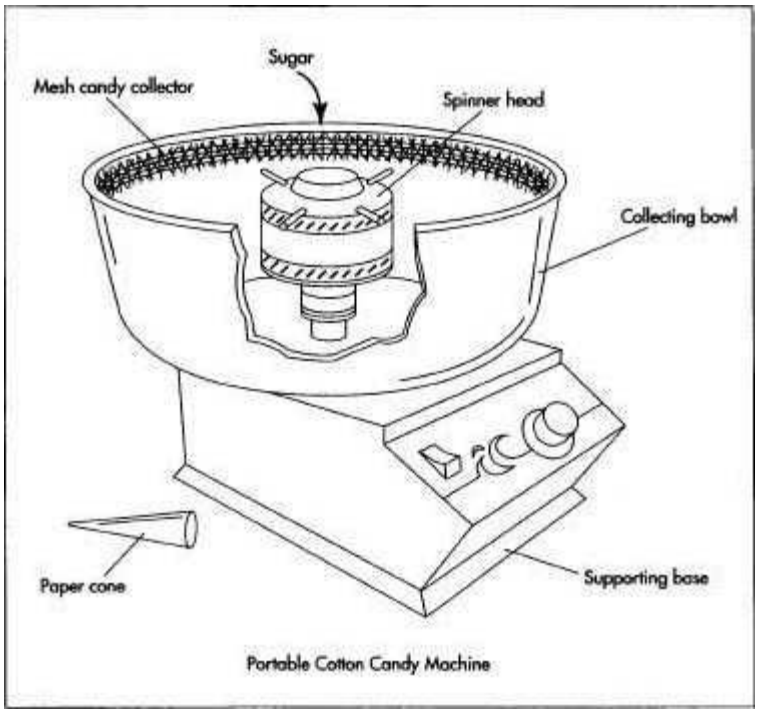

Figure no16. Cotton-candy process

Nanonization:

In this process, the particles of the drug are reduced in size to nanoparticles by milling the drug in the proprietary wet milling process. The agglomeration can be prevented by surface adsorption of the nanocrystals. These are then compressed and changed into a tablet. This technique is very useful for less water soluble drugs. The bioavailability of the drug is increased as the disintegration time is reduced to a significant extent [68].

Fast dissolving films:

In this technique, a non-aqueous solution is prepared containing water soluble film forming polymers (carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent

In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form [69].

Melt granulation:

Abdelbary prepared ODT by incorporating a hydrophilic waxy binder (super polystate) PEG6Sterate. Super polystate is a waxy material with a melting point of 33-370C. It is not only acts as a binder and increases the physical resistance of tablets, but also helps the disintegration of tablets as it melts in the mouth and solubilizes rapidly leaving no residue.

Advantages:

- Neither solvent nor water used in this process.
- Fewer processing steps needed thus time consuming drying steps eliminated
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.

Disadvantages:

- Requires high energy input
- Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials. [70].

Ion exchange resin Complexation technique:

Ion-exchange resins are vinyl, divinyl benzene and polystyrene copolymers available as high molecular weight polyelectrolytes having extensive charged functional sites. They are insoluble in nature and exchange their exchangeable ions with same charge ions in the surrounding ionic medium .A part from taste masking, resins have been used in modified drug release, drug stabilization, and tablet disintegration even in therapeutics too. Long-term physicochemical stability and safety of ion exchange resins have provided an additional benefit to consider them as drug carriers for a wide array of applications.

Bitter cationic drugs can get adsorbed onto the weak cation exchange resins of carboxylic acid functionality to form the complex, which is non-bitter. The complex of cationic drugs and weak cation exchange resin does not break at pH 6–7 of saliva with cation concentration of 40meq/l. But at high cation concentration and stomach pH of 1–3, free drug is immediately released [71].

General reaction of ion exchange resin complexation:

Re-So3 – Na+ + Drug+ Re-SO3 – Drug+ + Na+ 1

Re-N (CH3) + Cl– + Drug – Re-N (CH3) + Drug – + Cl – 2

Patented technologies for ODT's:

The main patented technologies for mouth dissolving tablets are as follows:

Zydis Tecnology:

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When Zydis units are put into the mouth, the freeze- dried structure disintegrates instantaneously and does not require water to aid swallowing. The Zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as Mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycine prevent the shrinkage of Zydis units during freeze drying process or long term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

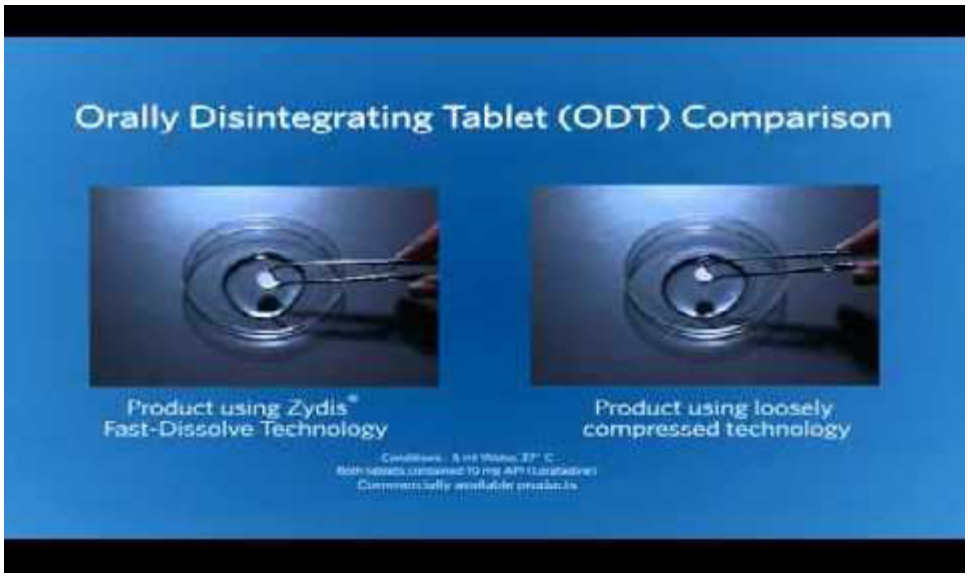

Figure no.17 Zydis Tecnology

Merits:

- Buccal pharyngeal and gastric regions are all areas of absorption from this formulation. Any
- Pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism.
- The Zydis formulation self-preserving because the final water concentration in the freeze dried
- Product is too low To\ allow for microbial growth.
- Patients who have difficulty swallowing oral medication due to dysphagia, stroke or medical
- Conditions such as gastro esophageal reflux disease, multiple sclerosis or Parkinson's disease.
- Pediatric patients.
- Patients who refuse or spit out oral medications, including patients with psychiatric or behavioral disorders.
- Companion animals such as dogs and cats

Demerits:

- The process of freeze-drying is a relatively expensive manufacturing process.
- The formulation is very lightweight and fragile, and therefore should not be stored in
- Backpacks or the bottom of purses.
- It has poor stability at higher temperatures and humidity's.
- The freeze-drying is time consuming process.
- It has poor physical resistance
- Loading of high dose of water-soluble drugs is not possible [72].

Orasolv technology:

This technology is patented by CIMA Labs. This includes use of effervescent disintegrating agents compressed with low pressure to produce the MDTs. The OraSolv process typically involves blending the microencapsulated API with magnesium oxide and mannitol to aid in the release of the drug from the polymeric coating. These micro particles are further blended with other excipients and loosely compressed to maintain some degree of tablet porosity to aid dispersion. Compression forces need to be kept to a minimum so as not to disrupt the API taste-masking coating. With OraSolv tablet technology, tablets are compressed to a hardness of 6-25 N and packaged in blister cards. The resultant tablet is relatively weak and friable and requires specific patented packaging technology (PakSolv, CIMA Labs) was developed to protect the tablets from breaking during transport and storage.

The OraSolv ODT technology uses taste-masked drug microparticles in a formulation that enhances tablet disintegration. On contact with saliva, the effervescent system promotes disintegration of the tablet. Carbon dioxide is generated by a reaction of the formulation components upon exposure to water (saliva in the mouth). This causes a sensation in the mouth that is pleasant to the patient and tends to stimulate further saliva reduction, which also aids in disintegration.

Advantages:

The OraSolv technology has been used for drug strengths in the range of 1 mg to 750 mg. Depending on formulation and tablet size, the disintegration time of the tablet can be designed in the range of 10 to 40 seconds

PakSolvR is a "dome-shaped" blister package that prevents the vertical movement of the tablet within the depressions, because the diameter of the lower portion of the dome is too narrow to accommodate the tablet. PakSolvR also offers light, moisture, and child resistance.

Disadvantages:

Both OraSolv and DuraSolv products are sensitive to moisture due to the presence of the effervescent system and must be packaged appropriately [73].

Durasolv technology:

The DuraSolv technology has a formulation similar to the OraSolv technology, combining taste masked drug micro particles with or without a low effervescence-containing formulation, was developed by CIMA labs, consist of a drug, fillers and the lubricants. The tablets are prepared by conventional tabletting equipment and have good rigidity. They can be packed in the conventional tabletting equipment and have good rigidity.

Advantages:

DuraSolv technology is good for tablets having low amount (125 mcg to 500 mg) of active ingredients and tablets are compressed to a greater hardness of 15-100 N, resulting in a more durable ODT. As a result, this technology enables packaging flexibility; tablets can be bottled and blistered.

Disadvantages:

The technology is not compatible with larger doses of active ingredients, because the formulation is subjected to high pressure during compaction. The drug powder coating in Durasolv may become fractured during compaction, exposing the bitter tasting drugs to the patient taste buds [74].

Wowtab technology:

Yamanauchi pharmaceutical company patented this technology. 'wow' means 'without water'. The WOW in the WOWTAB signifies the tablet is to be given without water. The active ingredients may constitute up to 50% w/w of the tablet. In this technique, saccharides of both low and high mould ability are used to prepare the granules. Mould ability is the capacity of a compound to be compressed. This technology utilizes sugar and sugar-like excipients. The two different types of saccharides having high mold ability like maltose, mannitol, sorbitol, and oligosaccharides (good binding property) and low mold ability like lactose, glucose, mannitol, xylitol (rapid dissolution) are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. Highly mould able substance has high compressibility and thus shows slow dissolution. The combination of high and low mould ability is used to produce tablets of adequate hardness [75].

Advantages:

- The Wowtab product dissolves quickly in 15 s or less.
- Wowtab product can be packed in both into conventional bottle and blister packs [75].

Flash dose technology:

This technology is patented by Fuisz. This system uses the combination of both Shearform and Ceform technologies in order to mask the bitter taste of the drug. A sugar based matrix, called 'Floss' is used, which is made up of a combination of excipients (crystalline sugars) alone or in combination with drugs. Nurofen meltlet, a new form of Ibuprofen, as a mouth-dissolving tablet is the first commercial product prepared by this technology and launched by Biovail Corporation.

Drawbacks

- The dosage form can accommodate only up to 600 mg of drug.
- Tablets produced are highly friable, soft and moisture sensitive. Therefore specialized packing is required. [76].

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Oraquick technology:

K. V. S. Pharmaceuticals have a patent over this technology. It utilizes taste masking microsphere technology called as micromask, which provides superior mouth feel over taste masking alternatives, significant mechanical strength, and quick disintegration/dissolution of product. Any kind of solvents are not utilized by taste masking process. Therefore it leads to superior and fast efficient production. [77].

Pharmaburst technology:

SPI Pharma, New Castle has a patent over this technology. It utilizes the coprocessed excipients to develop MDTs, which dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles [78].

Nanocrystal technology:

Elans, King of Prussia have a patent over this technology. This technology includes Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This method avoids manufacturing process such as granulation, blending, and tabletting, which is more advantageous for highly potent and hazardous drugs. As manufacturing losses are negligible, this process is useful for small quantities of drug.

Advantages:

- Pharmacokinetic benefits of orally administered nanoparticles (< 2 microns) in the form of rapidly disintegrating tablet matrix.
- Cost-effective manufacturing processes that utilize conventional, scalable unit operations.
- Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters).
- Wide range of doses (up to 200 mg of API per unit)[79].

Frosta technology:

A new technology called Frosta (Akina) was developed for making FMTs. The Frosta technology utilises the conventional wet granulation process and tablet press for cost-effective production of tablets. The Frosta tablets are mechanically strong with friability of < 1% and are stable in accelerated stability conditions when packaged into a bottle container. They are robust enough to be packaged in multi-tablet vials. Conventional rotary tablet presses can be used for the production of the tablets and no other special instruments are required. Thus, the cost of making FMTs is lower than that of other existing technologies. Depending on the size, Frosta tablets can melt in < 10 s after placing them in the oral cavity for easy swallowing. The Frosta technology is ideal for wide application of FMTs technology to various drug and nutritional formulations. [80].

Dispersible tablet technology:

Leks in Yugoslavia have a patent over this technology. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxine methane sulphonate was observed with dispersible tablets containing 0.8-10%, preferably about 4% by weight, of an organic acids. One of the essential excipients in the cimetidine formulation was a disintegrating agent. The disintegrating agents include starch or modified starches, microcrystalline cellulose, alginic acid, cross-linked sodium carboxymethyl cellulose, and cyclodextrin polymers. Dihydroergotoxine and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature [81].

Table No: 5 Marketed ODT tablet:

Nimulid-MD	Nimesulide	Panacea Biotech
Zyrofmeltab	Rofecoxib	ZydusCadila
MOSID-MD	Mosapride Citrate	Torrent Pharmaceuticals
Feledine Melt	Piroxicam	Pfizer
Maxalt ODT	Famotidine	Merck
Remeron Sol Tab	Mirtazapine	Organon
Romilast	Montelukast	Ranbaxy
Manza BDT	Olanzepine	Orchid
Olanexinstab	Olanzepine	Ranbaxy
Valus	Valdecoxib	Glenmark
Rofaday MT	Rofecoxib	Lupin
Torrox MT	Rofecoxib	Torrent
Dolib MD	Rofecoxi	Panacea
Zilflam	Rofecoxib	Kapron
Orthoret MD	Rofecoxib	Biochem
Nexus MD	Nimesulide	Lexus
Nimex MD	Nimesulide	Mexon healthcare
Nisure MD	Nimesulide	Suzen Pharma
Olnium MD	Nimesulide	Olcare Lab
Sulbid	Nimesulide	Alpic Remedies

LITRATURE REVIEW:

Velmurugan S *et al.*, (2010) reported that Oral drug delivery remains the most preferred route for administration of various therapeutic agents. Recent advances in technology prompted researchers and scientists to develop oral disintegrating tablets (ODTs) with improved patient convenience and compliance. ODTs are solid unit dosage form which dissolve or disintegrate rapidly in the mouth without water or chewing. Novel ODT technologies address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for pediatric, geriatric and psychiatric patients who have difficulty in swallowing (Dysphagia) conventional tablet and capsules. Technologies used for manufacturing of ODTs are either conventional technologies or patented technologies. This review depicts the various aspects of ODT formulation;superdisintegrants and technologies developed for ODT, along with various drugs explored, evaluation tests and marketed formulations in this field.

Suhagiya V. K. *et al.*, (2010) revealed that more than 50% of pharmaceutical products are orally administered for several reasons and undesirable taste is one of the important formulation problems that is Encountered with such oral products. Taste of a pharmaceutical product is an important parameter governing compliance. Hence taste masking of oral pharmaceuticals has become important tool to improve patient compliance and the quality of treatment especially in pediatrics. Different methods have been suggested for masking of taste of bitter drugs, which includes, coating of drug particles with inert agents, taste masking by formation of inclusion complexes, molecular complexes of drug with other chemicals, solid dispersion system, microencapsulation, multiple emulsions, using liposome's, Prodrugs and mass extrusion method but ion exchange resin is one of most extensively used method to overcome this problem. Ion-exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug-delivery vehicles. In the past few years, IER have been extensively studied in the development of novel drug-delivery systems (NDDSs) and other biomedical applications. Also recently the new applications of ion exchange resin like ophthalmic drug delivery, anti-deliquescence, improve solubility, and polymorphism has confirmed. This review highlights complete account of ion exchange resin and its application in drug delivery research are-discussed.

Shahi S.R. *et al*., (2008) revealed that etoricoxib is a novel, selective second generation cyclo-oxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug that is used for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. The poor aqueous solubility of the drug leads to variable dissolution rates. In the present investigation an attempt has been made to prepare oro-dispersible tablets of etoricoxib with enhanced dissolution rate. The another purpose of the present investigation was to evaluate effect of superdisintegrants like crospovidone (Polyplasdone XL), croscarmellose sodium (ac-di-sol) and sodium starch glycolate (Primojel) on dissolution of poorly soluble, selective COX-2 inhibitor in oro-dispersible tablets. In the study, the effect of superdisintegrants specifically at 2 and 4 % level in oro-dispersible tablet formulation on the *in vitro* dissolution was evaluated. These levels included optimum concentrations of selected superdisintegrants. It was concluded that oro-dispersible tablets of etoricoxib with enhanced dissolution rate can be made using selected superdisintegrants.

Rajnibala *et al*., (2012) reported that an oral solid dosage form should ideally disperse into the primary particles from which it was prepared. Tablets and capsules which need rapid disintegration, the inclusion of the right disintegrant is a prerequisite for optimal bioavailability. Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by decreasing the disintegration time which in turn enhances drug dissolution rate. Disintegrants are substances or mixture of substances added the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1- 10 % by weight relative to the total weight of the dosage unit. The present study comprises the various kinds of superdisintegrants which are being used in the formulation to provide focus on the safer, effective drug delivery with patient's compliance.

Rewar S *et al*., (2014) reported that now-a-days, orodispersible drug delivery systems are extensively used to improve bioavailability and patient compliance. Over the past three decades, orodispersible tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance, improved solubility and stability profiles. The purpose of the article is to review potential advancements of ODT technology in drug delivery applications. Various techniques employed to prepare ODTs include direct compression method, freeze drying and spray drying, tablet moulding,

sublimation and mass extrusion. ODTs could be preferred choice especially with those drugs sensitive to GI and for patients under category of pediatrics, geriatrics, bedridden, post-operative and who may have difficulty in swallowing the conventional tablets and capsules. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. ODTs render enhanced acceptability due to its patient compliance as well as improved bioavailability and stability. This article reviews recent trends undertaken to develop ODTs, new ODTs technologies

Margret chandira R *et al.,* (2010) reported that the demand for mouth dissolving tablets has been growing during the last decade especially for elderly and children who have swallowing difficulties. Etoricoxib is a new non-steroidal anti-inflammatory drug (NSAID) with selective cox-2 inhibitory activity, selective inhibition of cox-2 provides anti-inflammatory and analgesic activity it is commonly used for osteo-arthritis, rheumatoid arthritis, primary dysmenorrhea, post-operative dental pain and acute gout. The main criteria for mouth dissolving tablets are to disintegrate or dissolve rapidly in oral cavity with saliva in 15sec to 60sec with need of water. The disintegrant used should fulfill the criteria by disintegrating the tablets in specified time limit.in the present investigation variety of super disintegrant like primogel, kollidone, Ac-Di-sol, L-HPMC, L-HPC, were selected and tablets were prepared by direct compression method in different concentration like 4% and 8%. The prepared tablets were evaluated for weight variation, hardness, friability, *in vitro* disintegration time, wetting time, *in vitro* dissolution study, etc. formulation f-9 shows the lowest disintegration time (44sec) and wetting time (52sec). In vitrodissolution studies revealed that formulation F-9 containning 8% L-HPC showed 97% drug release at the end of 20min.

Jaysukh J *et al*., (2009) revealed that drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Over the past three decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance. ODTs are solid dosage forms containing medicinal substances which disintegrate rapidly, usually in a matter of seconds, when placed on the tongue. Products of ODT technologies entered the market in the 1980s, have grown steadily in demand, and their product pipelines are rapidly expanding. New ODT technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for paediatric,

geriatric, and psychiatric patients with dysphagia. This has encouraged both academia and industry to generate new orally disintegrating formulationsand technological approaches in this field. The aim of this article is to review the development of ODTs, challenges in formulation, new ODT technologies and evaluation methodologies, suitability of drug candidates, and future prospects.

Alok Kumar Gupta *et al*., (2011) suggested that the convenience of administration and improved patient compliance are important in the design of oral drug delivery system which remains the preferred route of drug delivery inspite of various disadvantages. One such problem can be solved in the novel drug delivery system by formulating "mouth dissolving tablets" (MDTs) which disintegrates or dissolves rapidly without water within few seconds in the mouth due to the action of superdisintegrant or maximizing pore structure in the formulation. Mouth dissolving tablets are advantageous particularly for pediatric, geriatric and mentally ill patients who have difficulty in swallowing conventional tablets and capsules. The review describes the various formulation aspects, superdisintegrants employed and technologies developed for MDTs, along with various excipients, evaluation tests, marketed formulation and drugs used in this research area.

Sharma Chandan, *et al.,* (2010) revealed that over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets with water among pediatric, geriatric, and psychiatric patients with dysphagia. Today, ODTs are more widely available as over-the-counter products for the treatment of allergies and cold and flu symptoms. Technologies used for manufacturing of orally disintegrating tablets are either conventional technologies or patented technologies. In conventional freeze drying, tablet molding, sublimation, spray drying etc. and in patented Zydis technology, Orasolv technology, Durasolv technology, Wow tab technology, Flashdose technology are important. Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. Evaluation of these tablets are done by following weight variation, friability, tensile strength, wetting time, and water absorption ratio

Muralidhar *et al*., (2010) found that Celecoxib is a selective cox-2 inhibitor is indicated to the treatment of osteoarthritis, rheumatoid arthritis, acute painful primary dysmenorrhoea. It is also superior to other NSAID's, due to lower incidences of symptomatic gastrointestinal ulcer complications than other NSAID's. Celecoxib is practically insoluble in water. The present investigation deals with enhancement of dissolution rate of celecoxib using mannitol as carrier with different techniques like physical mixtures, kneading method and solvent evaporation method. The dispersions were evaluated for drug content uniformity, dissolution rate study, T50, DE20, ANOVA. The FTIR & DSC were used to characterize solid state of solid dispersions. A marked increased in the dissolution rate was observed with all solid dispersions, among that celecoxib : mannitol (1:4) KM. Showed maximum drug release which was selected for formulation of tablets and evaluated for drug release characteristics. The promising formulation (F2) was then compared with existing marketed product, the release profiles was studied in water containing 2 % SLS. The release study showed that these are fast release formulations of celecoxib. So it is clearly evident that F2 and marketed product are greater than the pure drug .F2 subjected to stability studies the formulation was found to be stable for 4 weeks at 400c, with insignificant change in the hardness, disintegration time and *in-vitro* drug release pattern.

Seong Hoon Jeong *et al*., (2004) reported that fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several FDT technologies. The is review describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity. In particular, this review describes in detail FDT technologies based on lyophilization, molding, sublimation, and compaction, as well as approaches to enhancing the FDT properties, such as spray drying, moisture treatment, sintering, and use of sugar-based disintegrant. In addition, taste-masking technologies.

13. Yogyata S. Pathare *et al*., (2013) revealed that Current developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients. Oral thin film, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. Fast-

dissolving oral thin film is a solid dosage form, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing. Oral film includes various ingredients for its formulation which includes polymers, active pharmaceutical ingredient, film stabilizing agents, sweeteners, flavors, colors, saliva stimulating agents, preservatives, surfactants etc., but the first and far most a very essential ingredient which helps in film formation is a polymer. Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Water-soluble polymers are used as film formers for fast dissolving films. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. Fast-dissolving oral thin film offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices. In this review article the different polymers used for preparation of fast dissolving oral thin film like pullulan**,** gelatin**,** sodium alginate**,** pectin**,** rosin**,** starch**,** chitosan are discussed together with their physicochemical properties and film forming properties.

Priyanka Nagar *et al*., (2011) suggested that oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. Formulation of a convenient dosage form for oral administration, by considering swallowing difficulty especially in case of geriatric and pediatric patient leads to poor patient compliance. To troubleshoot such problems a new dosage form known as orally disintegrating tablet (ODT), has been developed which rapidly disintegrate & dissolve in saliva and then easily swallowed without need of water which is a major benefit over conventional dosage form. In addition, patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders prefer such preparation because they cannot swallow large quantity of water. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in such type of dosage form. The popularity and usefulness of the formulation resulted in development of several ODT technologies for preparation. The current article is focused on ideal characteristics, advantages and disadvantages, formulation aspects, formulation technologies, evaluation of products and future potential.

AshishGarg *et al*., (2013) reported that conventional dosage forms like tablets and capsules are now days facing the problems like dysphagia, resulting in the high incidence of non compliance and making the therapy ineffective. To obviate the problems associated with conventional dosage forms, mouth dissolving tablets have been developed having good hardness, dose uniformity, easy administration and serves as the first choice of dosage form for paediatrics, geriatrics and travelling patients. The MDTs were developed with an aim of having sufficient hardness, integrity and faster disintegration without water. Fast dissolving tablets are disintegrating and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds.

Sanjay Singh *et al*., (2009) revealed that Methods to improve patient's compliance have always attracted scientists towards the development of fancy oral drug delivery systems. Among them, mouth dissolving drug delivery systems (MDDDS) have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patent life. MDDDS have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. Therefore, these dosage forms have lured the market for a certain section of the patient population which includes dysphagia, bed ridden, psychic, geriatric and pediatrics patients. Several techniques have been developed in the recent past, to improve the disintegration quality of these delicate dosage forms without affecting their integrity. This article focuses on the technologies available and the advances made so far in the field of fabrication of mouth dissolving tablets.

J.R. Vane *et al*., (2002) suggested that cyclooxygenase (COX) is the pivotal enzyme in prostaglandin biosynthesis. It exists in two isoforms, constitutive COX- 1 (responsible for physiological functions) and inducible COX-2 (involved in inflammation). Inhibition of COX explains both the therapeutic effects (inhibition of COX-2) and side effects (inhibition of COX- 1) of non-steroidal anti-inflammatory drugs (NSAIDs). A NSAID which selectively inhibits COX-2 is likely to retain maximal anti-inflammatory efficacy combined with less toxicity. The activity of a number of NSAlDs has been investigated in several test systems,

showing that most of those marketed have higher activities against COX-1 or are equipotent against both isoforms. Adverse event data of marketed NSAIDs show a relationship between a poor safety profile and more potent inhibition of COX-1 relative to COX-2. There are several new non-steroidal COX-2 inhibitors in development. The most clinically advanced is meloxicam, which consistently demonstrates higher activity against COX-2 than COX- 1 in several test systems.

DaljitMasih1 *et al*., (2013) suggested that conventional dosage form such as tablets and capsules are the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing. However these dosage forms are facing problems like hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and in case of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance. To overcome these problems, mouth dissolving tablets have been developed, which having good hardness, dose uniformity, easy administration and serves as the first choice of dosage form for pediatrics, geriatrics and travelling patients. This report summarizes the details of ingredients used in preparation of mouth dissolving tablets; conventional manufacturing techniques for mouth dissolving tablets; patented technologies for preparation of mouth dissolving tablets; evaluation of mouth dissolving tablet; and mechanism of action of mouth dissolving tablets.

Jody K. Takemoto *et al*., (2008) reported that the NSAID etoricoxib is a selective inhibitor of cyclo-oxygenase 2 (COX-2), approved for treatment of patients with chronic arthropathies and musculoskeletal and dental pain. The rate of absorption of etoricoxib is moderate when given orally (the maximum plasma drug concentration occurs after ~1 hour), and the extent of absorption is similar with oral and intravenous doses. Etoricoxib is extensively protein bound, primarily to plasma albumin, and has an apparent volume of distribution of 120 L in humans. The area under the plasma concentration-time curve (AUC) of etoricoxib increases in proportion to increasing oral doses between 5 and 120 mg. The elimination half-life of ~20 hours in healthy subjects enables once-daily dosing. Etoricoxib iseliminated following biotransformation to carboxylic acid and glucuronide metabolites that are excreted in urineandfaeces, with little of the drug (<1%) being eliminated unchanged in the urine. Etoricoxib is metabolized primarily by the cytochrome P450 (CYP) 3A4 isoenzyme. Plasma concentrations (AUC) of etoricoxib appear not to be different in patients with chronic renal

insufficiency compared with individuals who have normal renal function. Compared with healthy subjects, it has been reported that the AUC is increased by approximately 40% in patients with moderate hepatic impairment. No inhibitory effects on CYP2C9, 2C19, 2D6, 2E1 or 3A4 are expected to occur with etoricoxib. Coadministration of etoricoxib with other drugs has been examined only to a limited extent, thus further assessment is necessary. Etoricoxib has been assessed for the management of several specific disease states, including pain, osteoarthritis, and rheumatoid arthritis, and has shown similar efficacy in comparison with traditional NSAIDs (including naproxen, diclofenac and ibuprofen) in these conditions. Etoricoxib has demonstrated a significant reduction in gastrointestinal toxicity compared with many traditional NSAIDs. The renal adverse effects of etoricoxib appear to be similar to those of other NSAIDs, and the cardiovascular adverse effects of this selective COX-2 inhibitor require further clinical scrutiny. Further study is necessary to delineate the relevance of the pharmacokinetic disposition in terms of the clinical benefits and risks of etoricoxib compared with other options in the clinical arsenal.

Masoom Raza Siddiqui *et al*., (2012) reported that the development of the pharmaceuticals brought a revolution in human health. These pharmaceuticals would serve their intended only if they are free from the impurities and are administered in appropriate amount. To make drugs serve their purpose various chemical and instrumentation method were developed at regular intervals which are involved in the estimation of drugs. These pharmaceuticals may develop impurities at various stages of their development, transportation and storage which makes the pharmaceutical risky to be administered thus it must be detected and quantitated.

Md. HasanuzzamanShohag *et al*., (2011) reported that the aim of this study was to compare the pharmacokinetic properties of two etoricoxib (CAS 202409-33-4) 60 mg formulations, namely Etocox-60. (test product) and reference product, and to evaluate whether these two formulations meet the FDA criteria to assume bioequivalence. Twenty-four healthy volunteers were enrolled into this randomized, single-dose, 2-way crossover, open-label pharmacokinetic study. Subjects were randomly assigned to receive the test formulation followed by the reference formulation or vice versa as a single dose of 60 mg tablets after 12 h overnight fasting, with a washout period of two weeks. Following oral administration, blood samples were collected at 0 (baseline), 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0, 48.0, 72.0, 96.0, and 120.0 h. Serum concentration of etoricoxib was assessed using a high performance liquid chromatographic- UV spectrometry procedure. The pharmacokinetic

parameters were determined by the non-compartmental method. After administering a single dose of 60 mg of each etoricoxib formulation, the obtained mean (SD) values for the test and reference products were 1.26 (0.33) and 1.29 (0.35) lg/ml for C_{max}; 3.25 (2.64) and 2.63 (1.40) h for t_{max}; 29.63 (8.31) and 30.40 (5.85) h · lg/ml for AUC0–120; and 31.84 (10.97) and 33.00 (8.10) h · lg/ml for AUC0–1, respectively. The mean t1/2 was found 27.99 (7.87) h and 29.84 (7.93)h for test and reference product respectively. From paired t-test, no significant differences were observed ($p > 0.05$) for any pharmacokinetic parameters. After analysis of variance, no period, sequence or formulation effects were observed for any pharmacokinetic property. The 90% confidence intervals of the test/reference mean ratios of the in-transformed $AUC_{0–120,}$ $AUC_{0–1}$ and C_{max} mean values were 95.90% (85.37%–107.74%), 94.69% (84.43%–106.20 %) and 97.87% (85.54%–111.98 %), respectively, which fell within the predetermined FDA bioequivalence range of 80%–125%. This single-dose study found that the test and reference formulations of etoricoxib met the regulatory criteria for bioequivalence in terms of both rate and extent of absorption.

Subhashis Chakraborty *et al*., (2009) reported that mouth dissolving tablets are well established dosage forms available in the market. The numerous advantages that they offer to the patients in terms of compliance as well as to the manufacturers in terms of huge revenues by line extension of products are well known. This article attempts to present a detailed review regarding technological advances made so far in the area of evaluation of mouth dissolving tablets with respect to special characteristics of these unique dosage forms. In the absence of any available standardized method, the author's recommendation on criticalissues in the field may be considered.

Patra S, *et al*., (2010) reported that the present study was carried out in order to mask the bitter taste of the etoricoxib by complexation with cation-exchange resin, Indion 204. The drug resin complexes (DRC) were prepared by batch process and efficient drug loading was obtained by using inactivated form of resin in the drug-resin ratio 1:3.3 with 30 min swelling time of resin in 25 mL of water with 5 min stirring time. Drug-resin complexes were characterized for dissolution studies and spectral studies. Drug release from drug-resin complex in salivary pH was insufficient to impart bitter taste. Volunteers rated the drug resin complex as tasteless and agreeable.

Inderbir Singh *et al*., (2010) reported that the etoricoxib is an antiinflammatory and analgesic agent in the treatment of arthritis, dysmenorrhoea, and acute dental surgery pain and is having a bitter taste. The present study is designed to mask the bitter taste of etoricoxib by complexation with weak cation exchange resins (Indion 214, 234 and 414) in order to increase its compatibility and patient compliance. Drug resinates were characterized by FTIR and XRD analysis methods. Drug resinates were evaluated by sensory taste evaluation test. Indion 234 resin was showing good taste masking ability compared to Indion 214 and 414. The *in vitro* drug release (after 60 minutes) was found to be 95%, 90% and 82% for F 234 III, F 414 III and F 214 respectively

David Rodrigues *et al., (*2003) suggested that etoricoxib (100 μCi/dose) was administered to six healthy male subjects (i.v., 25 mg; p.o., 100 mg). Following the i.v. dose, the plasma clearance was 57 ml/min, and the harmonic mean half-life was 24.8 h. Etoricoxib accounted for the majority of the radioactivity (~75%) present in plasma following both i.v. and p.o. doses. The oral dose, administered as a solution in polyethylene glycol-400, was well absorbed (absolute bioavailability of ~83%). Total recovery of radioactivity in the excreta was 90% (i.v.) and 80% (p.o.), with 70% (i.v.) and 60% (p.o.) excreted in urine and 20% in feces after either route of administration. Radiochromatographic analysis of the excreta revealed that etoricoxib was metabolized extensively, and only a minor fraction of the dose (<1%) was excreted unchanged. Radiochromatograms of urine and feces showed that the 6′-carboxylic acid derivative of etoricoxib was the major metabolite observed (≥65% of the total radioactivity). 6′-Hydroxymethyl-etoricoxib and etoricoxib-1′-*N*-oxide, as well as the *O*-β-D-glucuronide conjugate and the 1′-*N*-oxide derivative of 6′-hydroxymethyl-etoricoxib, were present in the excreta also (individually, ≤10% of the total radioactivity).

M. A. Radwan *et al.,* (2012) revealed that the effect of chronic administration of etoricoxib (EXB), in the absence or presence of St. John's Wort (SJW), on its pharmacokinetic parameters and blood pressure was investigated in rats. Methods: Rats were divided into 3 groups, each group received daily different oral treatment for 3 weeks. Rats' blood pressures were monitored initially, after 1 and 3 weeks of treatment, and after 1 week of discontinuing dosing of both drugs. EXB pharmacokinetic parameters in the absence or presence of SJW were calculated after 3 weeks. Key findings: SJW was significantly affected EXB pharmacokinetic parameters. The steady state peak plasma concentration and terminal half-life were reduced by 32 % and 91 %, respectively, due to a > 3 fold increase in its apparent

clearance which is a concentration and time dependent effect. EXB was significantly increased ($P < 0.001$) Rats' blood pressure while, co-administration of EXB and SJW was not significantly affect ($P > 0.05$) rats blood pressure as compared to the control. Conclusions: Monitoring blood pressure of patients anticipated taking EXB for extended period should be advised. The co-administration of SJW with EXB should be avoided since SJW would greatly reduce EXB concentrations by inducing its metabolism.

Takemoto *et al., (*2008) reported that the NSAID etoricoxib is a selective inhibitor of cyclo-oxygenase 2 (COX-2), approved for treatment of patients with chronic arthropathies and musculoskeletal and dental pain. The rate of absorption of etoricoxib ismoderate when given orally (the maximum plasma drug concentration occurs after ~1 hour), and the extent of absorption is similar with oral and intravenous doses. Etoricoxib is extensively protein bound, primarily toplasma albumin, and has an apparent volume of distribution of 120 L in humans. The area under the plasma concentration-time curve (AUC) of etoricoxib increases in proportion to increasing oral doses between 5 and120 mg. The elimination half-life of ~20 hours in healthy subjects enables once-daily dosing. Etoricoxib is eliminated following biotransformation to carboxylic acid and glucuronide metabolites that are excreted in urine and feces, with little of the drug (<1%) being eliminated unchanged in the urine. Etoricoxib is metabolized primarily by the cytochrome P450 (CYP) 3A4 isoenzyme. Plasma concentrations (AUC) of etoricoxib appear not to be different in patients with chronic renal insufficiency compared with individuals who have normal renal function. Compared with healthy subjects, it has been reported that the AUC is increased by approximately 40%in patients with moderate hepatic impairment. No inhibitory effects on CYP2C9, 2C19, 2D6, 2E1 or 3A4 are expected to occur with etoricoxib. Co administration of etoricoxib with other drugs has been examined only to a limited extent, thus further assessment is necessary. Etoricoxib has been assessed for the management of several specific disease states, including pain, osteoarthritis, and rheumatoid arthritis, and has shown similar efficacy in comparison with traditional NSAIDs (including naproxen, diclofenac and ibuprofen) in these conditions. Etoricoxib has demonstrated a significant reduction in gastrointestinal toxicity compared with many traditional NSAIDs. The renal adverse effects of etoricoxib appear to be similar to those of other NSAIDs, and the cardiovascular adverse effects of this selective COX-2 inhibitor require further clinical scrutiny. Further study is necessary to delineate the relevance of the pharmacokinetic disposition in terms of the clinical benefits and risks of etoricoxib compared with other options in the clinical arsenal.

James Klancke, *et al.,* (2003) reported that orally disintegrating tablets (ODT) are solid dosage forms that disintegrate in the oral cavity leaving an easy-to-swallow residue. The disintegration times are generally less than one minute. For orally disintegrating tablets, taste-masking of bitter or objectional-tasting drug substances is critical. The taste-masking aspect plays a significant role in dissolution method development, specifications, and testing. The USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets. Discriminating, robust dissolution methods are extremely useful for monitoring process optimization and changes during scale-up of taste-masked bulk drug and tablet manufacture.

Szakonyi G, et al ., (2013) revealed that one of the promising approaches to predict in vivo disintegration time of orally disintegrating tablets (ODT) is the use of texture analyzer instrument. Once the method is able to provide good *in vitro in vivo* correlation (IVIVC) in the case of different tablets, it might be able to predict the oral disintegration time of similar products. However, there are many tablet parameters that influence the *in vivo* and the in vitro disintegration time of ODT products. Therefore, the measured *in vitro and in vivo* disintegration times can occasionally differ, even if they coincide in most cases of the investigated products and the *in vivo* disintegration times may also change if the aimed patient group is suffering from a special illness. If the method is no longer able to provide good IVIVC, then the modification of a single instrumental parameter may not be successful and the in vitro method must be re-set in a complex manner in order to provide satisfactory results. In the present experiment, an optimization process was developed based on texture analysis measurements using five different tablets in order to predict their in vivo disintegration times, and the optimized texture analysis method was evaluated using independent tablets.

Johannes Kraemer, *et al.,* (2012) suggested that for industrially manufactured pharmaceutical dosage forms, product quality tests and performance tests are required to ascertain the quality of the final product. Current compendial requirements specify a disintegration and/or a dissolution test to check the quality of oral solid dosage forms. These requirements led to a number of compendial monographs for individual products and, at times, the results obtained may not be reflective of the dosage form performance. Although a general product performance test is desirable for orally disintegrating tablets (ODTs), the

complexity of the release controlling mechanisms and short time-frame of release make such tests difficult to establish. For conventional oral solid dosage forms (COSDFs), disintegration is often considered to be the prerequisite for subsequent dissolution. Hence, disintegration testing is usually insufficient to judge product performance of COSDFs. Given the very fast disintegration of ODTs, the relationship between disintegration and dissolution is worthy of closer scrutiny. This article reviews the current status of dissolution testing of ODTs to establish the product quality standards. Based on experimental results, it appears that it may be feasible to rely on the dissolution test without a need for disintegration studies for selected ODTs on the market.

Ugurlu T, *et al.,* (2015) This article summarizes the advantages of orally disintegrating tablets (ODTs) as well as critical issues during evaluation of ODTs such as bioequivalence and challenges and limitations of ODTs and finally present and the future of ODTs. ODTs have received ever increasing demand and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water. When ODTs are put on tongue they disintegrate instantaneously, releasing the drug which dissolve or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach. In such cases, bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both, industry and academia. Their growing importance has been underlined recently when European Pharmacopoeia adopted the term "Orodispersible Tablet" as tablet that is to be place in the mouth where it disperses rapidly before swallowing. ODTs have some challenges but solutions to overcome these challenges were shown in this paper.

Bhupendra G Prajapati, *et al.,* (2010) revealed that quetiapine fumarate bioavailability is 9%. Used in the treatment of schizophrenia. It is preferable to administer in the form of fast disintegrating tablets used for depressive episodes, acute manic episodes associated with bipolar I disorder at a short time. In present research work an attempt has been made to prepare taste masked fast dissolving tablets of quetiapine fumarate were prepared by using direct compression method. IR spectral analysis study showed that there was no drug interaction with formulation additives of the tablet. The blend was examined for the precompressional parameters results were within prescribed limits and indicated good free

flowing property. The prepared tablets formulations were evaluated for post-compressional parameters. All the post-compressional parameter are evaluated were prescribed limits and results were within IP acceptable limits. Taste evaluation was performed on six healthy human volunteers. The pure drug was felt bitter immediately after it was kept on the tongue and the sense was even carried upto 5 min. However the bitterness of the drug was reduced or even masked after complexation with Eudragit EPO in different ratios (1:0.5, 1: 1, 1:2, 1:3). In case of 1: 0.5 ratios it was felt slightly bitter after 1 min and it is apparent from the results that the increasing concentrations of the polymer have completely masked the bitter taste of the drug. The disintegration time of 72 to 241 sec, and in-vitro drug release showed 96.88 - 98.92% within 9 min. Formulation A3 showed 98.91% release after 30 min, B3 and C3 showed 102.83, 99.44 % drug release in release in 30 min and 19 min for both formulations respectively. The initial drug release for formulation C3 at 08 min is 79.62 %. From the above observations, it is concluded that crospovidone 15 % shows better drug release profile compared with other super disintegrants. So crospovidone was selected as best formulation. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. The results concluded that bitterness of the drug was masked and showing enhanced dissolution, improved effectiveness and hence better patient compliance.

Nalini Krishna Reddy M., *et al.,* (2012) suggested that the aim of the present research was to develop and evaluate taste masked orodispersible tablets (ODT) of naproxen. Over the past three decades, orally disintegrating tablets have gained considerable attention as a preferred alternative to conventional tablets due to better patient compliance. The most preferable route of drug administration (e.g. oral) is limited to drug candidate that show poor permeability across the gastric mucosa and those, which are sparingly soluble. A large majority of the new chemical entities and many new existing drug molecules are poorly soluble, thereby limiting their potential uses and increasing the difficulty of formulating bioavailable drug products. Formulations were prepared using different superdisintegrants such as crosscaramellose sodium, sodium starch glycolate, crosspovidone by direct compression method. The properties of the formulations such as porosity, hardness, friability, wetting time, water absorption ratio and disintegration time were investigated. All the formulations showed good flow properties, low weight variation with rapid disintegration time and *in-vitro* dissolution. The drug content of all the formulations was within the acceptable limits. The wetting time for F6 & F9 formulations was below one minute. Formulation F9 which contains 6% of crosspovidone showed least in- vitro disintegration time i.e., below 30 seconds and more than

90% drug release within 8 minutes. The in-vitro drug release of Naproxen ODT were best explained by Higuchi's equation as the plots showed the highest linearity follwed by first order and zero order, the Korsmeyer-Peppas release exponent "n" indicated that all formulations showed a mechanism of both diffusion and erosion mechanism so called anomalous(non- fickian) diffusion. The optimized formulation showed good *in-vivo* disintegration time and palatable taste. The excipients used in this study did not alter physicochemical properties of the drug, as tested by the Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimeter (DSC).

Ashwini Deshpande *et al.*, (2014) suggested that oral administration of any dosage form is most preferred route because of its self-medication, exact dosing of drug and easy administration but one important drawback of oral route is that the difficulty in swallowing in pediatric and geriatric patients and also the patients who have mental disorders. To overcome these problems developing oral disintegrating tablet which is disintegrate in mouth within 30 secs. The onset of action is also satisfactory. The drug ondansetron which is used as antiemetic in many situation like chemotherapy or radiotherapy induced emesis and also used in the early onset of alcoholism. In this formulation ondansetron is taste masked by polyethylene glycol 6000 because it is bitter drug. Many techniques used to formulate Oral Disintegrating tablets. This dosage form is formulated by sublimation technique in which Camphor is used as a sublimating agent. The prepared formulations were evaluated for precompressional and post-compressional parameters. The Drug-Excipient compatibility study was checked by UV for 15 days, these results indicated that there was no interaction between dug and excipients. The values of pre-compressional parameters like bulk density & tapped density were within acceptable limits and defined good free flowing properties. The hardness test of all the formulations describes acceptable mechanical strength (2.5 to 3.5 kg/cm2). Friability of all formulations was less than 1%. Drug content was found to be high (98.19 %- 105 %) and uniform in all the formulations. The tablet thickness was found to be 3.09 – 4.14 mm. The weight variation results indicated that average percentage deviation was less then ± 7.5 %, which provides good uniformity in all formulations. The disintegration time in preliminary trials declined significantly with surge in the concentration of superdisintegrant& subliming agent (up to 3.5% & 10% concurrently).The % Drug release from all formulation after 30 mins were within limit (> 96.40 %).

Patil C. *et al.,* (2011) revealed that the demand for orally disintegrating tablets of lamotrigine has been growing during the last decade especially for the geriatric and pediatric patients. Lamotrigine is a recognized drug for epilepsy, so development of an ODT of lamotrigine and to evaluate the effect of various superdisintegrants on its disintegration time and release profile was the prime objective of this research work. Tablets were prepared by direct compression technique using 3 different superdisintegrants. Sodium starch glycolate, croscarmellose sodium and crosspovidone XL-10 were used as superdisintegrants in combinations to achieve optimum release profile, disintegration time and hardness. Direct compression process was selected for this formulation of ODT tablets, because porous nature is more in direct compression blend than wet granulation blend, so it will give faster disintegration. Microcrystalline cellulose was used as diluent and mannitol, mint flavor and sodium saccharin were used to enhance the organoleptic properties of tablets. The tablets were evaluated for weight variation, hardness, friability, *in-vitro* disintegration time and drug release characteristics. Hardness and friability data indicated good mechanical strength around 3 kg/cm 2 for all the batches. The results of *in-vitro* disintegration time indicated that the tablets dispersed rapidly in mouth within 8s. Dissolution study revealed release rate of drug from the tablets was comparable with marketed tablet formulation of lamotrigine. It was concluded that superdisintegrants addition technique is a useful method for preparing orally disintegrating tablets by direct compression method.

Rakesh K. Patel1, *et al*., (2013) suggested that the objective of the current study was to develop and optimize an orally disintegrating tablet formulation of metoprolol tartrate which is an effective drug in the treatment of hypertension. Metoprolol tartrate orally disintegrating tablets were prepared by direct compression method using different ingredients such as mannitol, microcrystalline cellulose, aspartame, crospovidone, sodium starch glycolate, croscarmellose sodium, powder flavours strawberry, peppermint & orange, colloidal silicon dioxide and magnesium stearate. Tablets were evaluated for the physical properties, out of which disintegration time and wetting time were considered as responses in a 3 full factorial experimental plan. Results were statistically examined using design expert software and polynomial mathematical equations; found to be statistically significant) for disintegration time and wetting time data. The obtained results were used to generate optimized overlay plot. The physical data from the numerical optimization were verified and found to be very close to those predicted from the regression analysis. Accelerated stability study was also

performed on the optimum formulation. All results were in accordance with the requirements of a orally disintegrating tablet.

Mohammad Ali Shahtalebi, *et al*., (2015) suggested that the difficulty in swallowing is common among all age groups, especially elderly and pediatrics. Orally disintegrating tablets may constitute an innovative dosage form that overcome the problem of swallowing and provide a quick onset of action. This study was aimed to formulate and evaluate an orally disintegrating tablet (ODT) containing ondansetron while using semisynthetic and natural superdisintegrants. Methods: Orodispersible tablets were prepared by direct compression using natural superdisintegrant (Karaya gum) and semi-synthetic superdisintegrant (croscarmellose). The prepared tablets were evaluated for hardness, friability, thickness, drug content uniformity, water absorption and wetting time. A 32 factorial design was used to investigate the effect of independent variables (amount of croscarmellose and karaya gum) on dependent variables (disintegration time, friability and Q5 [cumulative amount of drug release after 5 minutes]). A counter plot was also presented to graphically represent the effect of independent variable on the disintegration time, friability and Q5 . The check point batch was also prepared to prove the validity of the evolved mathematical model. The systematic formulation approach helped in understanding the effect of formulation processing variable. Results: According to the results of optimized batches, the best concentrations of superdisintegrant were as follows: 7.88 mg Karaya gum and 7.78 mg croscarmellose gave rapid disintegration in 31 seconds which showed 99% drug release within 5 minutes. Conclusion: Karaya gum, a natural superdisintegrant, gives a rapid disintegration and high release when used with synthetic superdisintegrant in formulation of ODT.

Vinay Jain, *et al., (* 2012) suggested that a fast dissolving tablet was prepared by using various Ingredients like crosepovidone , mannitol Sodium lauryl sulphate (SLS) , Magnesium stearate was taken in different concentration (5-10% 50%, 2-6%, 1%,).Chemical incompatibility studies confirmed that there is no interaction between drug and excipients used in the formulations. All the batches are prepared by direct compression method. Effect of disintegrants concentration on the disintegration behavior was evaluated, and all the tablets were evaluated for hardness, friability, weight variation, water absorption ratio, dissolution, and assay. Among the all preparations F8 emerged as the best formulation and showed maximum dissolution rate.

Rakhee K Kotecha, ***et al.,*** **(2017)** suggested that a dosage forms that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention and hence Fast disintegrating oral drug delivery system was developed. The present study was aimed at formulation and evaluation of Metoclopramide Hydrochloride Oro-Dispersible Tablets. Metoclopramide hydrochloride a derivative of paraaminobenzoic acid is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux and for the prevention of cancer chemotherapy- induced emesis. Oro-dispersible tablets of Metoclopramide Hydrochloride was prepared by masking the bitter taste by Aminoalkyl methacrylate copolymer (Eudragit EPO), indion 294 ion exchange resin and cyclodextrin in different concentration. All the batches were prepared by direct compression method. All the batches of ODTS were evaluated for appearance, thickness, weight variation, hardness, friability, in-vitro disintegration time, in-vitro dispersion time, wetting time, content uniformity, in-vitro dissolution study. The stability studies for optimized formulation (F15) were performed for 3 Months and then tablets were evaluated. The results obtained were satisfactory and complies with the pharmacopeial specifications.

Etoricoxib

Etoricoxib are also called non-steroidal anti-inflammatory drugs (NSAIDs), or sometimes just 'anti-inflammatories'. Etoricoxib eases pain and swelling (inflammation) in conditions like osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, and it may also be used for short periods of time in gout.

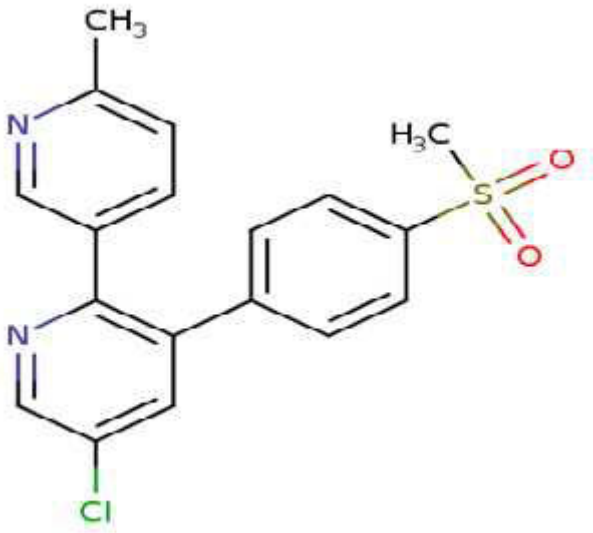


Figure no. 18 Structure of Etoricoxib

Chemical Name:

5-Chloro-3-(4-methanesulfonyl-phenyl)-6'-methyl-[2,3'] bipyridiny

Etoricoxib, [5-chloro-2-(6-methylpyridin-3-yl)-3-(4-methylsulfonylphenyl) pyridine], is a novel orally active agent that selectively inhibits cyclooxygenase-2 (COX-2). Etoricoxib is used in the treatment of Rheumatoid arthritis, osteoarthritis, acute gout, chronic musculoskeletal pain (including chronic low back pain), postoperative dental pain and primary dysmenorrhoea. The drug is available as oral tablets, and the recommended dosage is between 60 and 120 mg/day. It is a poorly soluble, lipophilic drug with estimated logP of 3.14 and pKa of 4.6. Etoricoxib behaves like a weak base. Its aqueous solubility is low and highly pH-dependent. Pharmacokinetic studies, however, show that when administered orally, etoricoxib is completely and rapidly absorbed, with an oral bioavailability of up to 100%.

BCS OF ETORICOXIB:

Etoricoxib, a widely prescribed anti-inflammatory drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility.

COX-2 Inhibitors:

Prostaglandins are made by two different enzymes cyclooxygenase-1 (cox-1) and cyclooxygenase-2 (cox-2). The prostaglandins made by the two different enzymes have slightly different effect on the body. Cox-2 inhibitors are NSAIDs that selectively block the cox-2 enzyme and not the cox-1 enzyme. Blocking this enzyme impedes the production of prostaglandins by the cox-2 which is more often the cause the pain and swelling of inflammation and other painful condition. Because they selectively blocking the cox-2 enzyme and not the enzyme, these drug are uniquely different form traditional NSAIDs which usually both cox-1 and cox-2 enzymes.

Table No. 6 Drug profile:

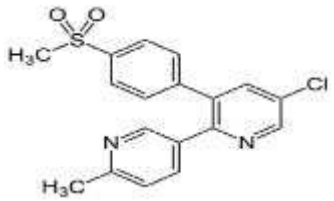
Drug name	**Etoricoxib**
Synonyms	Etonian, Etonitazene, Etoolin, Etoricoxib,
Drug state	Solid,
Drug type	Small molecule
Category	Rheumatoid arthritis, Ankylosing spondylitis treatment
Chemical name	5-Chloro-3-(4-methanesulfonyl-phenyl)-6'-methyl-[2,3'] bipyridiny
Cas number	202409-33-4
CHEMICAL STRUCTURE  Etoricoxib	
Chemical formula	$C_{18}H_{15}ClN_2O_2S$
Drug brand	Alcox Ecoxpic , Tory Torcxia,
Mechanism of action	Like any other COX-2 selective inhibitor Etoricoxib selectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2). This reduces prostaglandins (PGs) generation from arachidonic acid.
Route of administration	Oral

Table No. 7 Physicochemical Properties:

Appearance	White to off-white powder
Molecular weight	358.842 g/moL
Solubility	Etoricoxib is freely soluble in methanol, tetrahydrofuran, dimethyl sulfoxide, methyl ethyl ketone, dimethyl formamide, and chloroform.
Melting point	134^0C
PKa (strong acid)	19.69
PKa (strong base)	4.49
Storage	Stored in a well closed container in a cool, dry place.
Absorption	Approximately 75%
Protein binding	92%
Biological half life	22 hours
Water solubility	0.00328 mg/ml
Site and mechanism of action	COX-2 INHIBITORS
Available dosage forms	30, 60, 90, 120,
Adverse reactions	Diarrhea swelling of the legs, ankles or feet. High blood pressure. Dizziness headache.
Use	Acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis

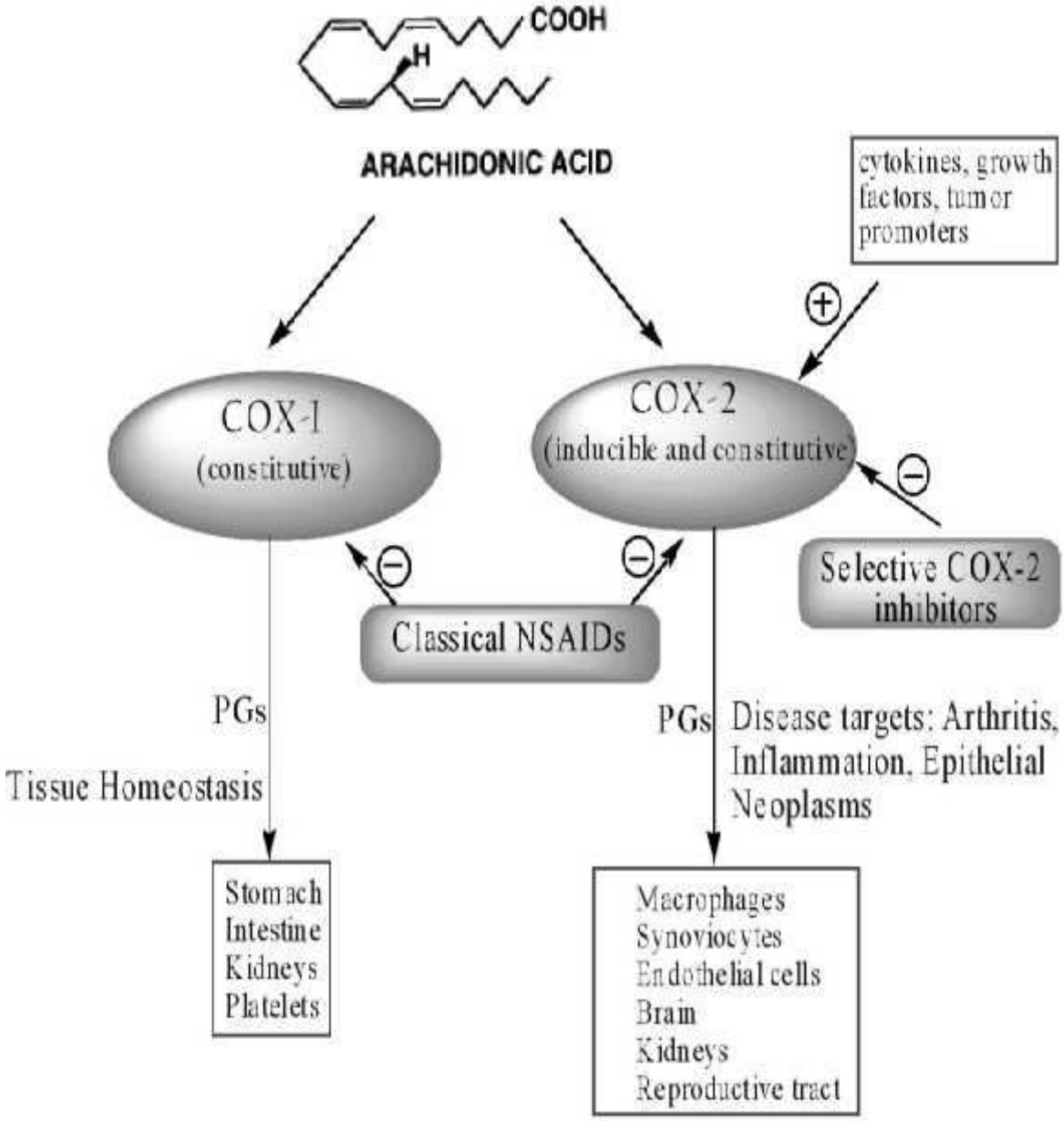


Figure no. 19 cox-2 mechanism actions

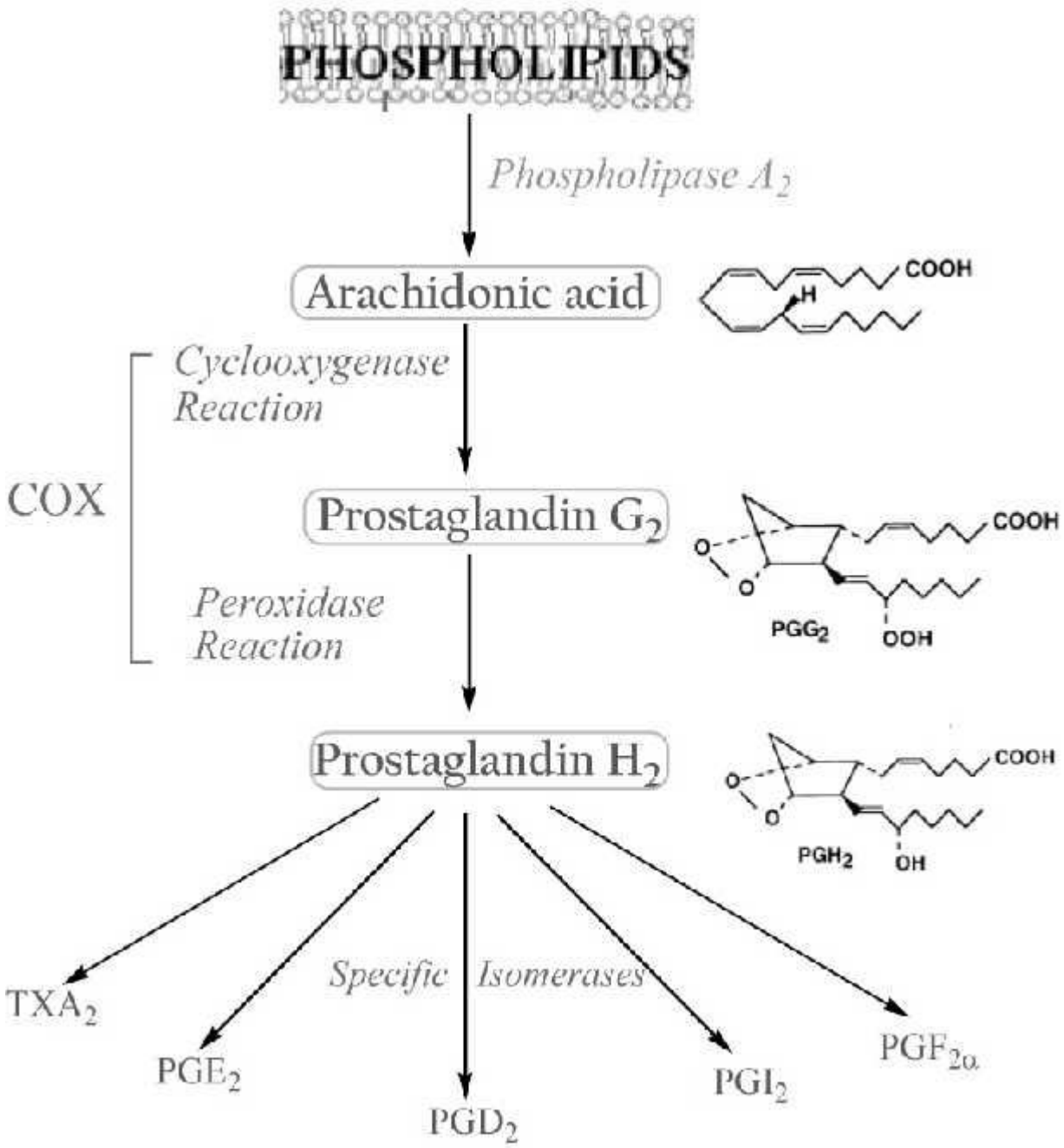


Figure no. 20 cox-2 working

Background:

Etoricoxib is a nonsteroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgestic, and antipyretic properties. It is approved for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute pain. Etoricoxib has also shown promise in prevention of cancer, and has been used as an adjunct to surgery to reduce the number of adenomatous colorectal polyps in patients with the hereditary colon cancer susceptibility syndrome, familial adenomatous polyposis (FAP). The anti-inflammatory and painrelieving properties of etoricoxib result from inhibition of prostaglandin (PG) synthesis by selective inhibition of PG G/H synthase-2 (encoded by gene PTGS2).

The two PTGS isoforms, PTGS1 and PTGS2, are bisfunctional enzymes with both cyclooxygenase (COX) and hydroperoxidase activities, but they are commonly referred to as COX. Etoricoxib is a member of the subclass of NSAIDs, which were purposefully designed as COX-2-selective inhibitors (pdCOX-2 inhibitors) and that are frequently called coxibs. Most traditional NSAIDs (tNSAIDs) inhibit both COX isoforms however, some of them show a degree of COX-2 selectivity that is similar to that of celecoxib, although they were developed before COX-2 was discovered. PdCOX-2 inhibitors provide anti-inflammatory effects that are comparable with tNSAIDs that inhibit both COX isoforms while reducing the risk of serious gastrointestinal toxicity. Following its introduction to US market in December 1998, etoricoxib quickly became one of the most frequently prescribed drugs for the relief of pain and inflammation. However, the data supporting a favorable gastrointestinal toxicity profile were much weaker than those of other compounds within the class. Etoricoxib, as well as other selective and nonselective NSAIDs, have been under intense scrutiny since 2004, when two pdCOX-2-selective inhibitors, rofecoxib and valdecoxib, were withdrawn from the market due to an increased risk of cardiovascular events including myocardial infarction.

Celocoxib and lumiracoxib were never approved in the US due to cardiovascular safety concerns. Etoricoxib is the only pdCOX-2 inhibitor currently available in the US. For many patients with both severe arthritis and intolerance to nonselective NSAIDs due to gastrointestinal side effects, pdCOX-2 inhibitors provide significant clinical benefit. The clinical care of patients requiring anti-inflammatory pain therapy, as well as those at high risk of colorectal adenomas, would be greatly aided by measurements that identify the patients who will benefit from etoricoxib, yet not suffer adverse events. This summary briefly reviews the pharmacokinetics of etoricoxib and discusses the candidate genes mediating the diverse pharmacological profile of etoricoxib. Knowledge of the pharmacogenomics of these pathways may help to achieve personalization and optimization of etoricoxib therapy.

Pharmacokinetics:

After oral administration, etoricoxib is rapidly absorbed and achieves peak serum concentration in approximately 3hrs. It is extensively metabolized in the liver, with very little drug (<3%) being eliminated unchanged. The major routes of excretion for celecoxib are feces and urine. Etoricoxib is metabolized primarily through methyl hydroxylation to form hydroxyetoricoxib. This reaction is largely catalyzed by CYP2C9, although CYP3A4 also plays a minor (<25%) role. Hydroxetoricoxib is further oxidized to form carboxyetoricoxib by cytosolic alcohol dehydrogenases ADH1 and ADH2, and then conjugated with glucuronic acid by UDP glucuronosyltransferases to form the 1-Oglucuronide. None of the metabolites are pharmacologically active.

As etoricoxib metabolism is predominantly mediated by CYP2C9, polymorphisms in CYP2C9 are likely to have a direct impact on etoricoxib pharmacokinetics and variability in drug responses. Individuals who are poor metabolizers of CYP2C9 substrates (e.g. CYP2C93 allele carriers) have an increased exposure to etoricoxib when compared with those with normal CYP2C9 activity. Drugs that inhibit CYP2C9 should therefore be used with caution in patients taking etoricoxib. Although not a substrate of CYP2D6, etoricoxib inhibits this metabolic enzyme. Drugs that are metabolized by CYP2D6 (e.g. metoprolol) should also be used with caution in patients receiving etoricoxib due to potential risk of drug interaction.

Example of celocoxip hepatocyte:

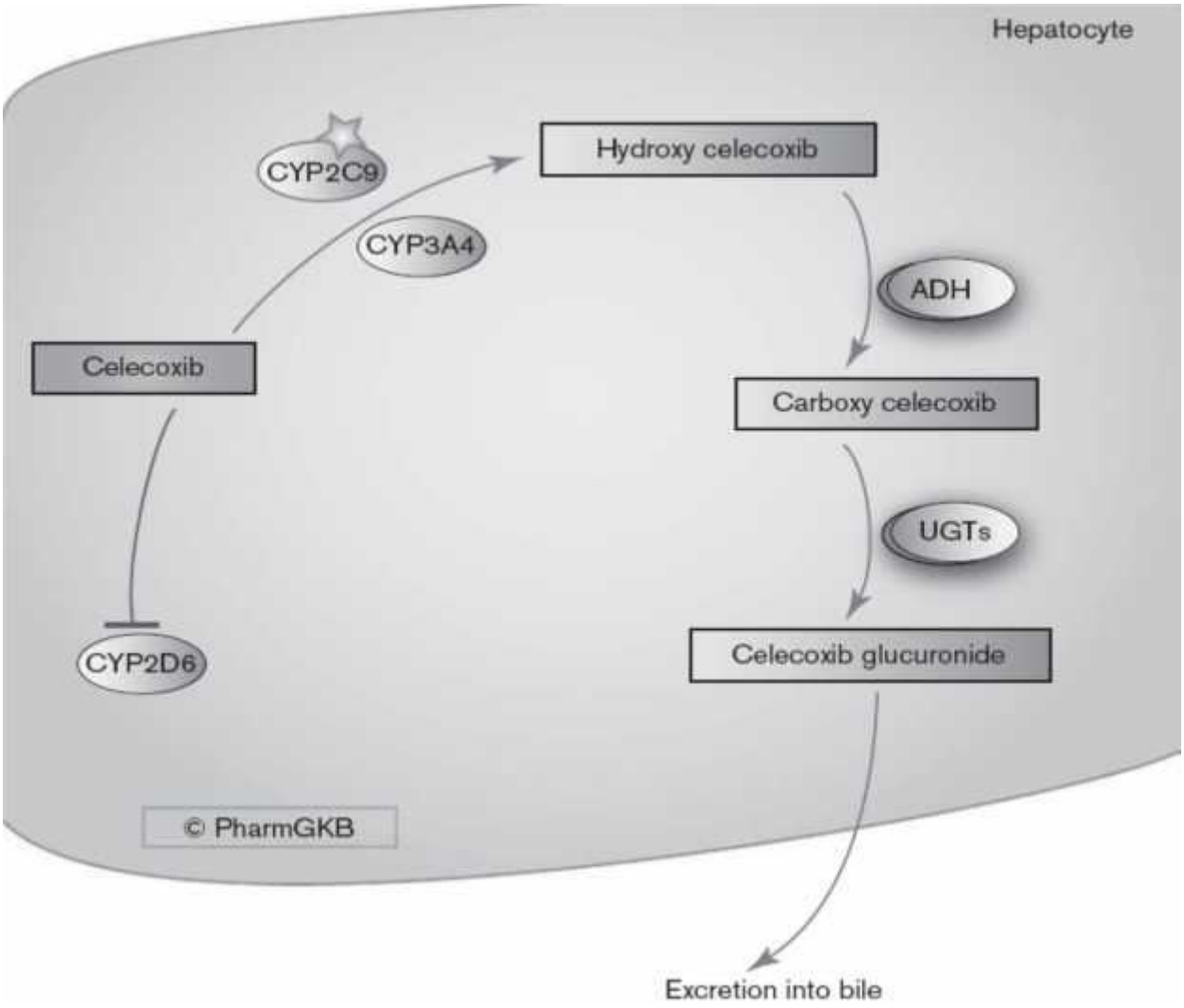


Figure no. 21 process of hepatocyte

Pharmacodynamics:

Etoricoxib exerts its anti-inflammatory and analgesic activities through blocking the synthesis of various inflammatory prostanoids (PG). The prostanoids, which include PGs and thromboxane, are the end products of fatty acid metabolism produced by tissue specific COX enzymatic activity. These products are important physiological and pathological mediators that are involved in a wide range of biological processes including inflammation, pain, cancer, glaucoma, osteoporosis, cardiovascular diseases, and asthma. The production of the prostanoids

(PG) is dependent on the availability of arachidonic acid (AA). Following stimulation of the cell membrane by inflammatory or mitogenic signals, the first step in PG synthesis is the release of AA from the cellular phospholipids through the action of either secretory (sPLA2, encoded by gene PLA2G2A) or cytoplasmic (cPLA2, encoded by gene PLA2G4A) phospholipases. Once AA is released, the two isoenzymes, COX-1 (encoded by PTGS1) and COX-2 (encoded by PTGS2), catalyze the production of the prostanoids. As indicated above, this involves two sequential reactions. The initial COX reaction converts AA into PGG2. The second reaction reduces PGG2 to PGH2. PGH2 is then converted into active metabolites PGE2, prostacyclin (PGI2), thromboxane (TxA2), PGD2, and PGF2a by the action of tissue-specific PG syntheses. These active metabolites interact with specific prostanoid G-protein-coupled receptors to mediate diverse physiological responses, such as inflammation, fever, blood pressure regulation, clotting, and gastrointestinal protection.

The COX-1 and COX-2 enzymes exhibit distinct expression profiles and roles in physiological processes. COX-1 is constitutively expressed in many cell types and is the major COX isoform in gastric tissue. It is responsible for the protection of the gastric mucosa, which led to the development of the 'COX-2 hypothesis' that drugs targeted against COX-2 only would have reduced upper gastrointestinal toxicity. Although COX-2 is highly inducible by inflammatory stimuli such as cytokines, growth factors, and tumor promoters [28–31], it is also constitutively expressed in some tissues, such as the vessel wall, the kidney, or the heart. Indeed, the depression of the physiological formation of COX-2-dependent prostanoids in these tissues has been identified as the molecular mechanism underlying the thrombotic cardiovascular complications of COX-2 inhibition. Seven placebo-controlled, randomized trials with three chemically distinct pdCOX-2 inhibitors, including etoricoxib, have documented the cardiovascular risk. Of note, etoricoxib is now used at lower doses than in the trials that showed its cardiovascular hazard. etoricoxib has 30-fold greater inhibitory activity against COX-2 compared with COX-1, and inhibits COX-1 only minimally at therapeutic concentrations. Although the selectivity for COX-2 measured in vitro is lower for etoricoxib compared with other drugs in the coxib class (e.g. rofecoxib, valdecoxib, lumiracoxib, and celocoxib), it is very similar at therapeutic concentrations in vivo. Etoricoxib also retains more ability to inhibit COX-1 compared with other coxibs; however, the consequences of this with regard to its therapeutic efficacy and toxicity are not well understood

Cardiovascular toxicity:

Data from clinical trials and case–control studies have been associated the use of selective COX-2 inhibitors, rofecoxib, valdecoxib, and etoricoxib with an increased incidence of myocardial infarction, stroke, and death due to cardiovascular causes. These toxicities were uncovered as secondary endpoints during trials testing coxibs for colorectal adenoma prevention and arthritis treatment. The US Food and Drug Administration currently mandate black-box warnings of increased cardiovascular hazards for the entire NSAIDs class.

Available data suggest that this risk may increase with the duration of use and may also vary by a patient's individual baseline cardiovascular risk. For etoricoxib, the increased cardiovascular risk seems to be exposure dependent; both the dose and the dosing interval may be important factors in cardiovascular risk. In the Adenoma Prevention with etoricoxib (APC) trial, etoricoxib twice a day exhibited a greater than three-fold risk for combined endpoints of cardiovascular death, myocardial infarction, stroke, or heart failure compared with placebo, and 200mg twice a day with a greater than two-fold risk.

Patients with higher baseline cardiovascular risk factors also tended to exhibit an increased risk. An evaluation of 5-year outcome data from the APC trial found a significant association between baseline cardiovascular risk factors and etoricoxib associated cardiovascular events. The prevention of colorectal sporadic adenomatous polyps trial showed that the risk for cardiac disorders was higher in those taking etoricoxib 400mg once daily than in those on placebo. In contrast, a number of clinical studies and a meta-analysis failed to demonstrate clear evidence of an increased thrombotic cardiovascular risk with etoricoxib doses of less than or equal to 400mg daily compared with placebo.

These analyses included data comparing coxibs with other nonselective NSAIDs. It is unclear whether nonselective NSAIDs also increase cardiovascular risk; therefore, these data cannot assess the relative safety of coxibs. In a more conclusive study, a pooled analysis of six randomized trials comparing etoricoxib with placebo concluded that cardiovascular risk for

etoricoxib-treated patients increases with dose, and that a once-daily dose is associated with lower cardiovascular risk than the twice daily dose.

Patients in the high baseline cardiovascular risk group exhibited a disproportionately higher risk of an adverse event, whereas etoricoxib did not cause a significant increase in cardiovascular events in the low-risk group, suggesting the importance of considering baseline cardiovascular risk for appropriate patient selection. In response to these data, the American Heart Association recommends that patients treated with etoricoxib use the lowest effective dose for the shortest duration to minimize the potential risk for an adverse cardiovascular event. Patients with existing cardiovascular disease or risk factors for cardiovascular disease may be at greater risk and alternative therapy should be considered. The mechanism underlying the increased cardiovascular risk of COX-2 inhibition has been studied extensively.

The clinical events associated with coxib cardiovascular toxicity are primarily thrombotic in nature. The depression of COX-2-derived cardioprotective PGs, particularly PGI2, and perhaps PGE2, by the coxibs removes a physiological restraint on mediators that induce thrombosis, increase blood pressure, and promote a therogenesis. One of these mediators is TxA2, which is synthesized by COX-1 action in platelets. Long term treatment with COX-2-specific inhibitors may create a prothrombotic environment and predispose patients to belevated cardiovascular risk. This may be particularly harmful for patients already predisposed to thrombosis due to the presence of atherosclerotic plaques in coronary or cerebral arteries. It is likely that the clinical safety of etoricoxib may depend on a fine balance of multiple factors, especially given the complexity of the molecular system regulating a therothrombotic processes. Interindividual variability in drug metabolism, differences in the half-life of the drug, the effect on blood pressure, or endothelial function may all contribute to the toxicity profile of coxibs or other NSAIDs

Table no. 8 EXCIPIENT PROFILE OF POLACRILIN POTASSIUM

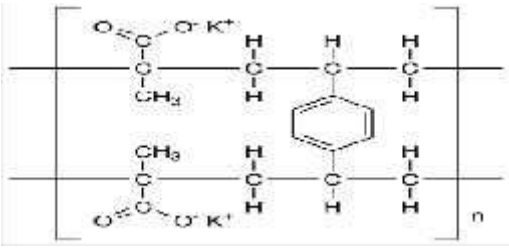
Synonyms	Divenyl benzene, potassium methacrylate polymer, polacrilin potassium, indion 294
Chemical formula	$(C_{10}H_{10}.C_4H_6O_2.K)$ X-
Description	It is a very fine , white to grayish-white odorless, crystalline
Functional categories	Ion exchange resin
Solubility	Insoluble in water
Moisture content	≤10
Melting point	242.5 m^2/g
storage	It is stable and should be stored in a well closed container in a cool, dry place.
application	Tablet disintegrant, taste masking, product meet specs of polacrilin potassium.
Chemical structure	

Table no .9 EXCIPIENT PROFILE OF TARTARIC ACID

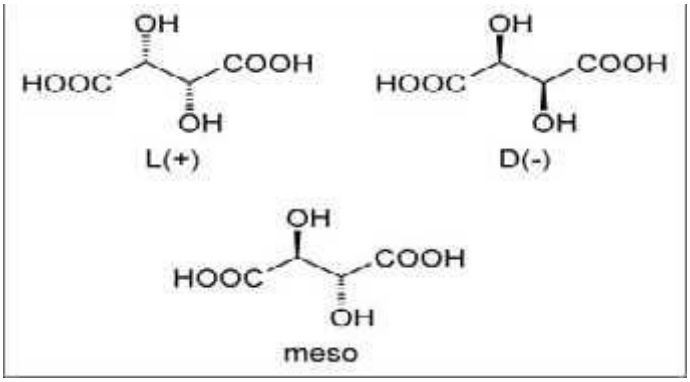
Synonyms	Erythraric acid, tartaric acid, uvic acid, paratartaric acid
Chemical formula	$C_4H_6O_6$
Description	White crystalline powder
Functional categories	Leavening agents, buffering agents
Solubility	Soluble in water
Melting point	171-174^{0}C
Stability storage conditions	Should be stored in a well closed container in a cool place.
Incompatibilities	Acetic acid, chromic acid glycol, nitric acid, hydroxyl compounds, perchloric acid,
Application	It used to food additives,
Chemical structure	

Table no.10 EXCIPIENT PROFILE OF PEARLITOL FLASH

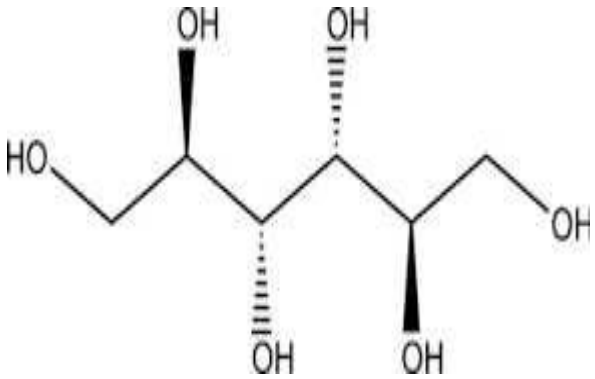
synonyms	D- mannital, mannite, unitolo M 200 , isotol, pearlitol sd 200, osmosal,
Chemical formula	$C_6H_{14}O_6$
Description	White crystalline powder
Functional categories	OH
Melting point	167-170^{0}C
Stability and storage conditions	Storied in a well closed container in a cool and dry place,
application	Anti- caking agents, free flowing agents, stabilizer, diluents,
Chemical structure	

Table no.11 EXCIPIENT PROFILE OF CROSPOVIDONE

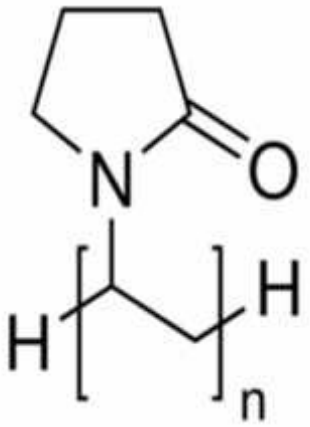
Synonyms	Poly vinyl pyrolidone, crospovidone, povidone,
Chemical formula	C_6H_9NO
Descriptions	White color fine powder , tasteless, odorless,
Functional categories	Disintegrating agents,
Solubility	Insoluble in PVP, Soluble in water,
Melting point	150^0C
Stability and storage conditions	Stored in a well closed container in a cool place,
Chemical structure	

Table no. 12 EXCIPIENT PROFILE OF CROSCARMELLOSE SODIUM

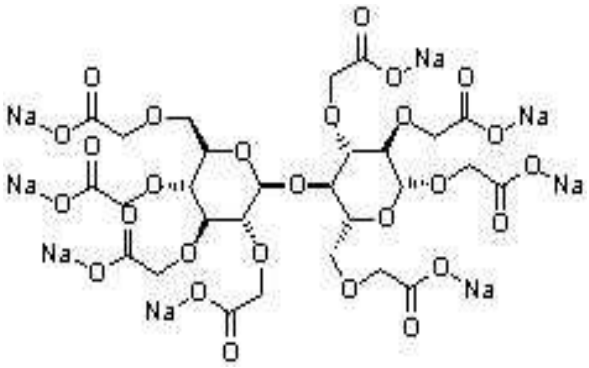
Synonyms	Sodium carboxymethyl cellulose, croscarmellose sodium,
Chemical formula	$C_{28}H_{30}Na_8O_{27}$
Description	White crystalline powder
Functional categories	Disintegrating agents
Melting	150-170^{0}C
Stability and storage	Stored in a well closed container in a cool dry place
Chemical structure	

Table no. 13 EXCIPIENT PROFILE OF SUCRALOSE

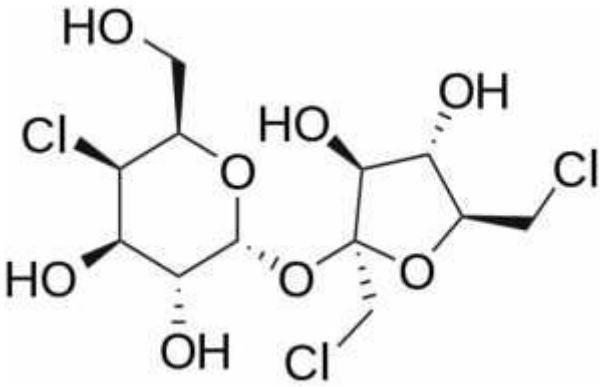
Synonyms	Sucktastic , sucralfate, surase-isomaltase
Chemical formula	$C_{12}H_{19}Cl_3O_8$
Description	White crystalline powder
Functional categories	Sweetening agents
Solubility	Water
Melting point	125^0C
Stability storage	Stored in a well closed container
Molar mass	397.64g/mol
Chemical name	1,6-dichloro -1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy- α-D-galactopyranoside,
Chemical structure	

Table no.14 EXCIPIENTS PROFILE OF TALC

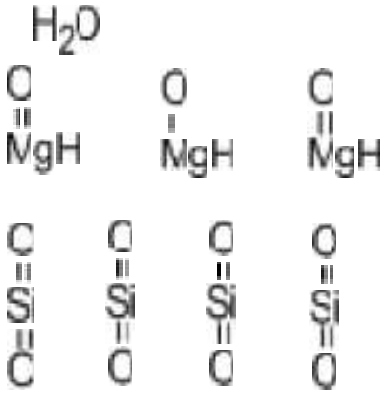
Synonyms	Talcum powder, mineral , soaprock, talc, French chalk, steatite
Chemical formula	$Mg_3Si_4O_{10}(OH)_2$
Description	Colorless
Functional categories	Lubricant
Chemical name	Hydrous magnesium silicate
Solubility	Insoluble in water, slightly soluble in dilute mineral acids
Melting point	1500^0C
Molecular weight	379.259g/mol
Chemical structure	

Table no.15 EXCIPIENTS PROFILE OF MAGNESIUM STEARATE

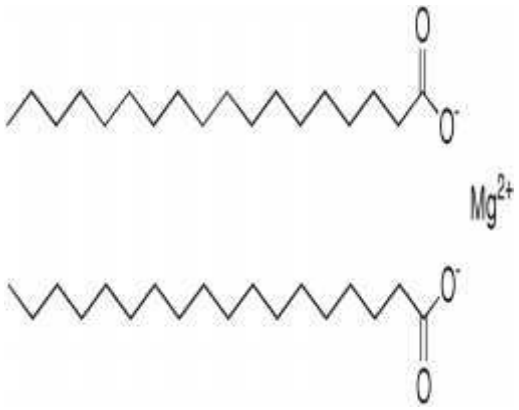
Synonyms	Dolomol , magnesium stearate
Chemical formula	$Mg(C_{18}H_{35}O_2)_2$
Description	White color
Functional categories	Lubricant
Molecular weight	591.27 g/mol
Solubility	Soluble in water, slightly soluble in benzene
Melting point	88.5^0C
Chemical structure	

Table no.16 EXCIPIENTS PROFILE OF NEOTAME

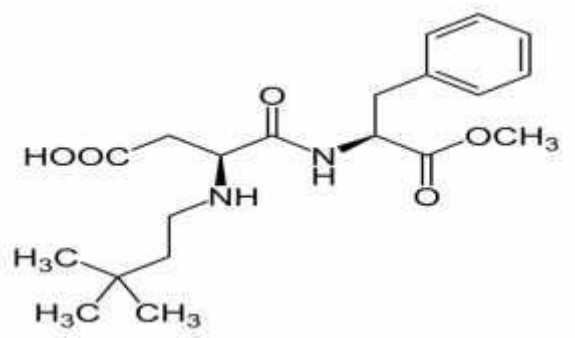
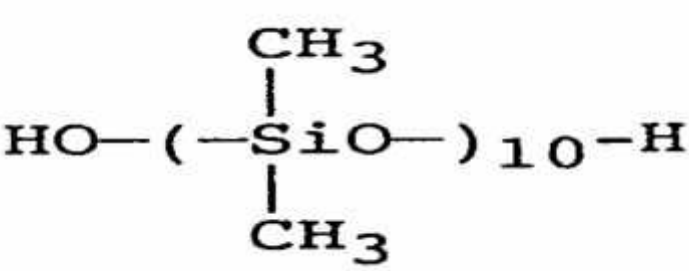
Synonyms	Neotame, neostriatal, neostriatum, neosystems,
Chemical formula	$C_{20}H_{30}N_2O_5$
Functional categories	Sweetening agents
Description	White crystalline powder
Melting point	81.00-84.00^{0}c
Chemical name	(s)-3-((3,3diethylbutyl)amino)-4-(((s)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobutanic acid
Chemical structure	

Table no.17 EXCIPIENTS PROFILE OF AEROSIL

Synonyms	Aerosil ,aerosol, aerosinusitis
Chemical name	Dioxosilane
Molecular formula	Sio_2
Description	White color fine powder
Molecular weight	60.08 g/mol
Functional categories	Bulking agents
Melting point	1610^0C (2930^0F)
Chemical structure	

DISEASE PROFILE

Etoricoxib is used for relieving pain and swelling of joints associated with Osteoarthritis. Etoricoxib is used for relieving swelling, stiffness, and pain of joints caused due to Rheumatoid arthritis. Etoricoxib is also used for the symptomatic treatment of ankylosing spondylitis.

The main difference between osteoarthritis and rheumatoid arthritis is the cause behind the joint symptoms. Osteoarthritis is caused by mechanical wear and tear on joints. Rheumatoid arthritis is an autoimmune disease in which the body's own immune system attacks the body's joints.

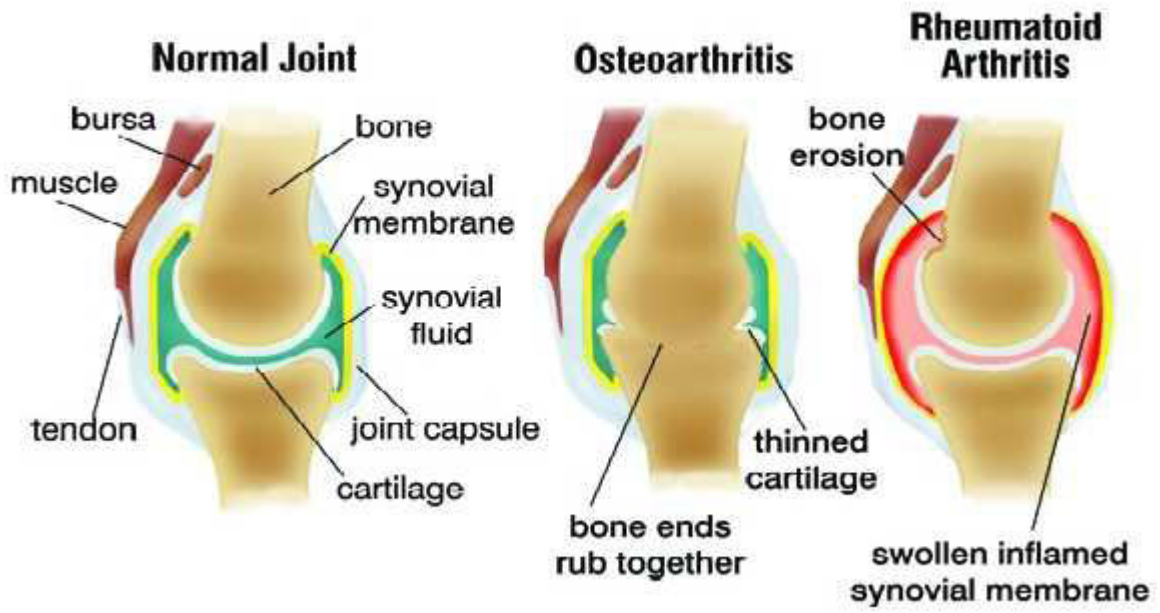


Figure no. 22 Osteoarthritis bone

Osteoarthritis:

Osteoarthritis (also known as OA) is a common joint disease that most often affects middle-age to elderly people. It is commonly referred to as "wear and tear" of the joints, but we now know that OA is a disease of the entire joint, involving the cartilage, joint lining, ligaments, and bone. Although it is more common in older people, it is not really accurate to say that the joints are just “wearing out.” It is characterized by breakdown of the cartilage (the tissue that cushions the ends of the bones between joints), bony changes of the joints, deterioration of tendons and ligaments, and various degrees of inflammation of the joint lining (called the synovium).

This arthritis tends to occur in the hand joints, spine, hips, knees, and great toes. The lifetime risk of developing OA of the knee is about 46%, and the lifetime risk of developing OA of the hip is 25%, according to the Johnston County Osteoarthritis Project, a long-term study from the University of North Carolina and sponsored by the Centers for Disease Control and Prevention (often called the CDC) and the National Institutes of Health.

Osteoarthritis is a top cause of disability in older people. The goal of osteoarthritis treatment is to reduce pain and improve function. There is no cure for the disease, but some treatments attempt to slow disease progression.

Symptoms:

Osteoarthritis (OA) is caused by aging joints, injury, and obesity. OA symptoms include joint pain and stiffness. Treatment depends on the affected joint, including the hand, wrist, neck, back, knee, and hip, and involves medication and exercise. If you are overweight, weight loss may improve OA symptoms.

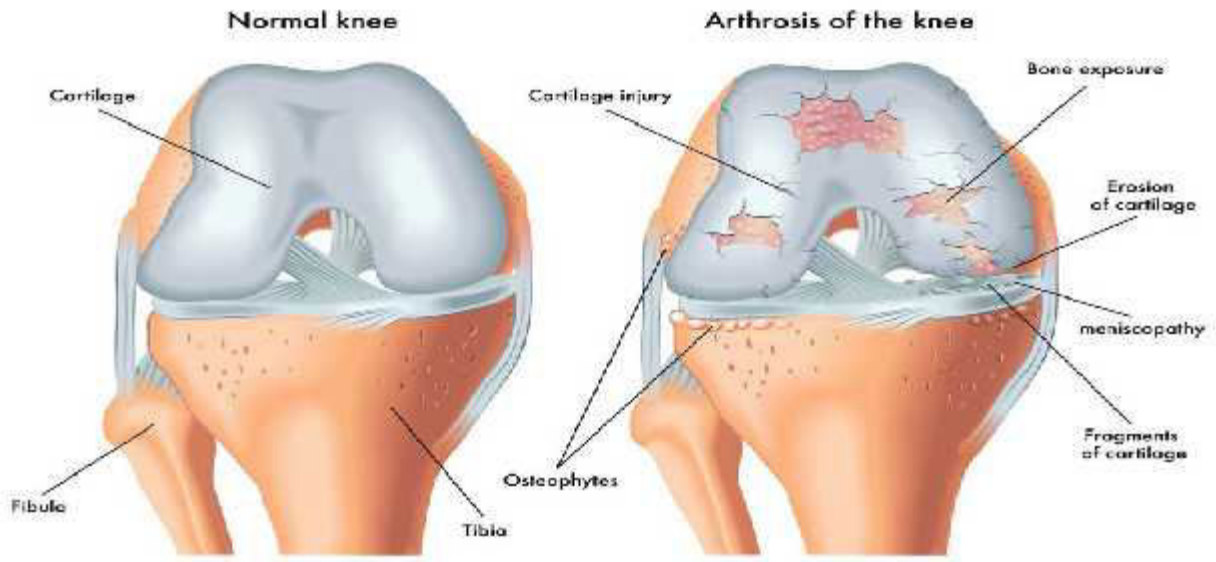


Figure no. 23 Osteoarthiritis erosion of bone

How do you treat osteoarthritis?

There is no proven treatment yet that can reverse joint damage from OA. The goal of osteoarthritis treatment is to reduce pain and improve function of the affected joints. Most often, this is possible with a mixture of physical measures and drug therapy and, sometimes, surgery.

Physical measures: Weight loss and exercise are useful in OA. Excess weight puts stress on your knee joints and hips and low back. For every 10 pounds of weight you lose over 10 years, you can reduce the chance of developing knee OA by up to 50 percent. Exercise can improve your muscle strength, decrease joint pain and stiffness, and lower the chance of disability due to OA. Also helpful are support ("assistive") devices, such as orthotics or a walking cane, that help you do daily activities. Heat or cold therapy can help relieve OA symptoms for a short time.

Certain alternative treatments such as spa (hot tub), massage, and chiropractic manipulation can help relieve pain for a short time. They can be costly, though, and require repeated treatments. Also, the long-term benefits of these alternative (sometimes called complementary or integrative) medicine treatments are unproven but are under study.

Drug therapy: Forms of drug therapy include topical, oral (by mouth) and injections (shots). You apply topical drugs directly on the skin over the affected joints. These medicines include capsaicin cream, lidocaine and diclofenac gel. Oral pain relievers such as acetaminophen are common first treatments. So are nonsteroidal anti-inflammatory drugs (often called NSAIDs), which decrease swelling and pain.

In 2010, the government (FDA) approved the use of duloxetine (Cymbalta) for chronic (long-term) musculoskeletal pain including from OA. This oral drug is not new. It also is in use for other health concerns, such as mood disorders, nerve pain and fibromyalgia.

Patients with more serious pain may need stronger medications, such as prescription narcotics. Joint injections with corticosteroids (sometimes called cortisone shots) or with a form of lubricant called hyaluronic acid can give months of pain relief from OA. This lubricant is given in the knee, and these shots may help delay the need for a knee replacement by a few years in some patients.

Surgery:

Surgical treatment becomes an option for severe cases. This includes when the joint has serious damage, or when medical treatment fails to relieve pain and you have major loss of function. Surgery may involve arthroscopy, repair of the joint done through small incisions (cuts). If the joint damage cannot be repaired, you may need a joint replacement.

Supplements:

Many over-the-counter nutrition supplements have been used for osteoarthritis treatment. Most lack good research data to support their effectiveness and safety. Among the most widely used are calcium, vitamin D and omega-3 fatty acids. To ensure safety and avoid drug interactions, consult your doctor or pharmacist before using any of these supplements. This is especially true when you are combining these supplements with prescribed drugs

Rheumatoid arthritis:

Rheumatoid arthritis (RA) is an autoimmune disease in which the body's immune system – which normally protects its health by attacking foreign substances like bacteria and viruses – mistakenly attacks the joints. This creates inflammation that causes the tissue that lines the inside of joints (the synovium) to thicken, resulting in swelling and pain in and around the joints. The synovium makes a fluid that lubricates joints and helps them move smoothly.

If inflammation goes unchecked, it can damage cartilage, the elastic tissue that covers the ends of bones in a joint, as well as the bones themselves. Over time, there is loss of cartilage, and the joint spacing between bones can become smaller. Joints can become loose, unstable, painful and lose their mobility. Joint deformity also can occur. Joint damage cannot be reversed, and because it can occur early, doctors recommend early diagnosis and aggressive treatment to control RA.

Rheumatoid arthritis most commonly affects the joints of the hands, feet, wrists, elbows, knees and ankles. The joint effect is usually symmetrical. That means if one knee or hand if affected, usually the other one is, too. Because RA also can affect body systems, such as the cardiovascular or respiratory systems, it is called a systemic disease. Systemic means "entire body.

Figure no. 24 Rheumatoid arthritis bone

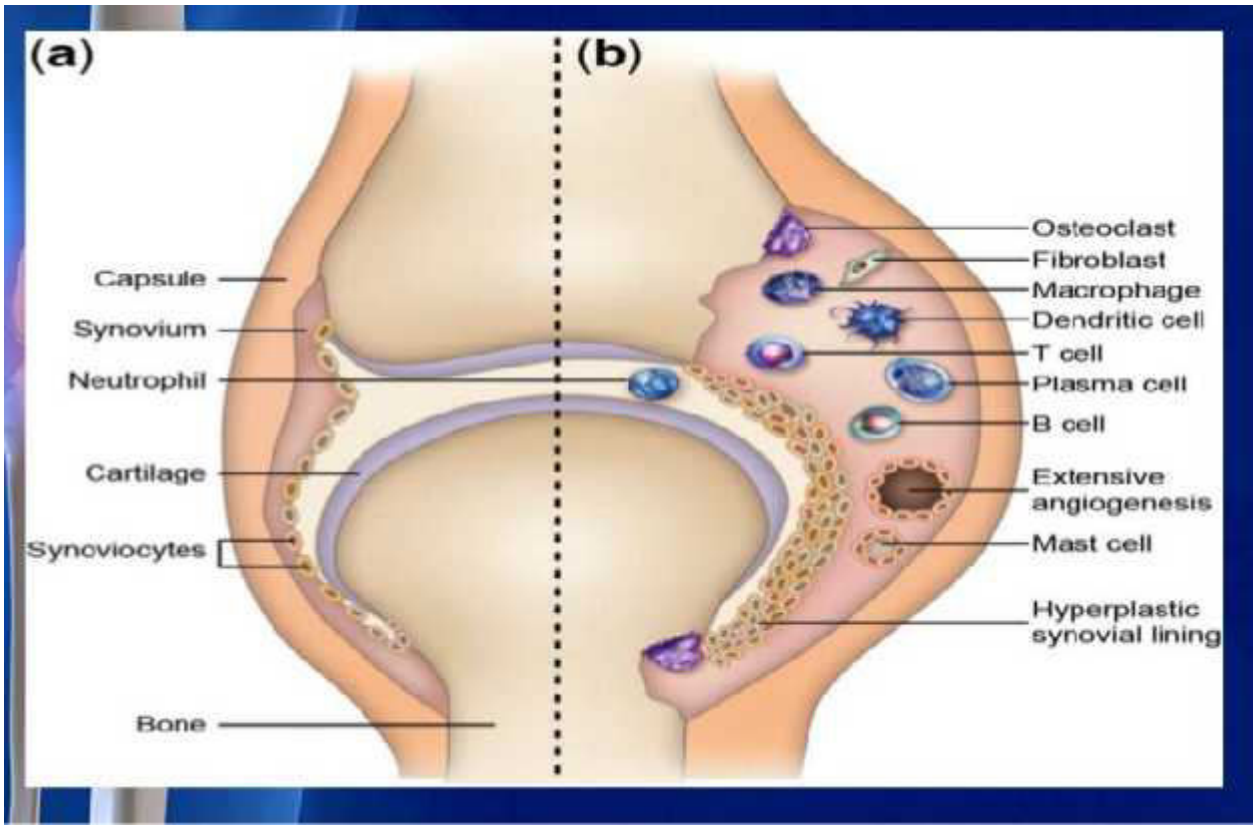


Figure no. 25 Rheumatoid arthritis of bone damage by immune system

Rheumatoid arthritis affected joint:

Here, the joint is inflamed due excess influx and accumulation of cells and fluid in the synovium. The result is that the synovium appears red and swollen due to the production of extra fluid. The swelling can cause the bone to erode into the joint space. Additionally, the affected joint feels warm due to increased blood flow to this region. The joint starts paining due to the following causes:

- The inflammation induces chemical production that affects the nerve endings.
- The synovial capsule gets stretched as a result of joint swelling.

The capsule continues to remain stretched despite bringing down the inflammation and cannot effectively perform its function of anchoring the joint in place. This causes the joint to

move abnormally without restraint. The joint becomes injured upon inflammation and gradually gets destroyed upon repeated inflammation. In most cases, more than one joint is affected. Often, the same joint is affected on both sides of the body.

Symptoms of Rheumatoid Arthritis:

Symptoms of Rheumatoid Arthritis appear on and off. If symptoms grow, it could mean that the condition has become severe.

The typical symptoms of Rheumatoid Arthritis include:

- Joint pain accompanied by swelling.
- Stiffness
- Feeling fatigued and tired, depressed or irritable.
- Anemia
- Flu-like symptoms: Fever and sweating.

Certain rare symptoms include:

- Weight loss
- Eye inflammation
- Rheumatoid nodules (lumps of flesh found on the elbows or hands and feet).
- On rare occasions, inflammation in other parts of the body: lungs, blood vessels and membranes lining the heart.

Lifestyle factors that could result in Rheumatoid Arthritis:

- Smoking
- Consuming high amounts of red meat
- Drinking a lot of coffee

Further, certain genetic factors can increase the risk of developing Rheumatoid Arthritis. Additionally, symptoms seem to worsen in cold weather although the weather in itself does not seem to impact disease development

Diagnosis:

It would be advisable to seek help from a Rheumatologist- a doctor specialized in the methods and techniques to diagnose and treat Rheumatoid Arthritis.

The Rheumatologist will probably perform blood tests and X-rays to help identify the extent of damage and the course of future medication.

Ankylosing spondylitis:

Ankylosing spondylitis is a type of arthritis that affects the spine. Ankylosing spondylitis symptoms include pain and stiffness from the neck down to the lower back. The spine's bones (vertebrae) fuse together, resulting in a rigid spine

Ankylosing spondylitis is a form of chronic inflammation of the spine and the sacroiliac joints. The sacroiliac joints are located at the base of the low back where the sacrum (the bone directly above the tailbone) meets the iliac bones (bones on either side of the upper buttocks) of the pelvis. Chronic inflammation in these areas causes pain and stiffness in and around the spine, including the neck, middle back, lower back, and buttocks. Over time, chronic inflammation of the spine (spondylitis) can lead to a complete cementing together (fusion) of the vertebrae, a process referred to as ankylosis. Ankylosis causes loss of mobility of the spine.

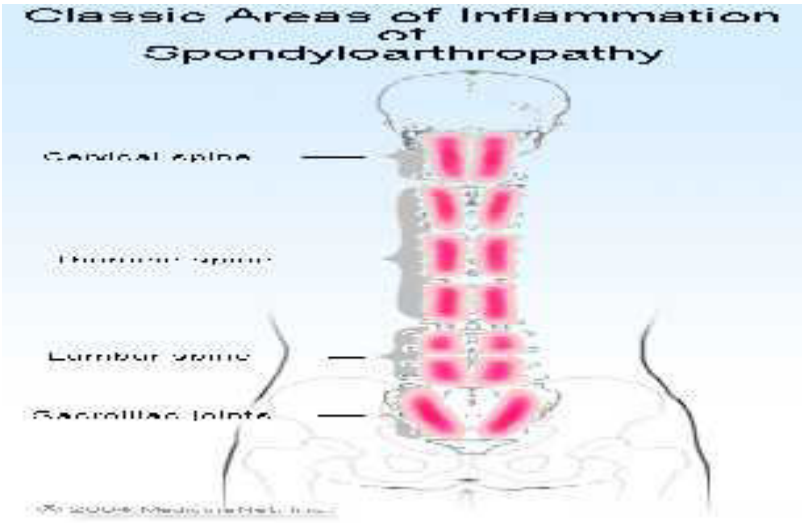


Figure no. 26 Ankylosing spondylitis

The most common early symptoms of ankylosing spondylitis include:

- **Pain and stiffness.** Constant pain and stiffness in the low back, buttocks, and hips that continue for more than three months. Spondylitis often starts around the sacroiliac joints, where the sacrum (the lowest major part of the spine) joins the ilium bone of the pelvis in the lower back region.
- **Bony fusion.** Ankylosing spondylitis can cause an overgrowth of the bones, which may lead to abnormal joining of bones, called "bony fusion." Fusion affecting bones of the neck, back, or hips may impair a person's ability to perform routine activities. Fusion of the ribs to the spine or breastbone may limit a person's ability to expand his or her chest when taking a deep breath.
- **Pain in ligaments and tendons.** Spondylitis also may affect some of the ligaments and tendons that attach to bones. Tendonitis(inflammation of the tendon) may cause pain and stiffness in the area behind or beneath the heel, such as the Achilles tendon at the back of the ankle.

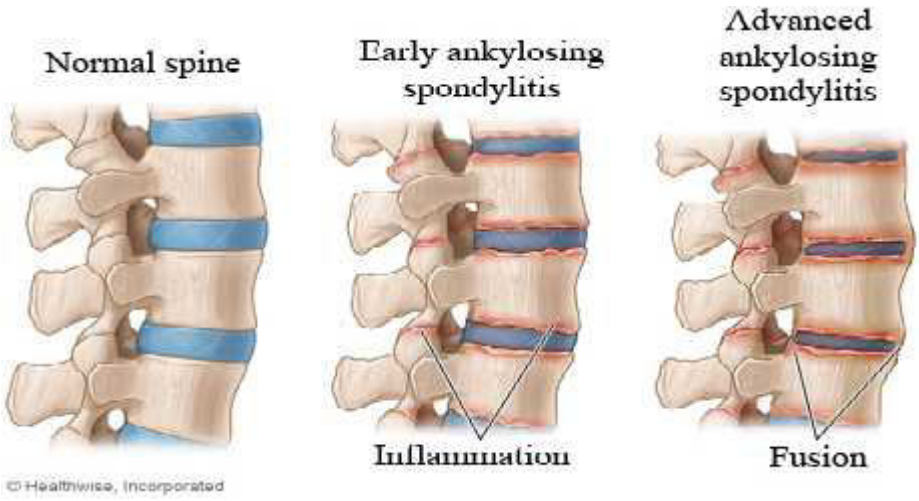


Figure no. 27 Ankylosing spondylitis bone damage

How Is Ankylosing Spondylitis Diagnosed?

The diagnosis of ankylosing spondylitis is based on several factors, including:

- Symptoms Findings of a physical exam X-rays of the back and pelvis
- Measurements of the chest when breathing
- Results of lab tests

How is Ankylosing Spondylitis Treated:

There is no cure for ankylosing spondylitis, but there are treatments that can reduce discomfort and improve function. The goals of treatment are to reduce pain and stiffness, maintain a good posture, prevent deformity, and preserve the ability to perform normal activities. When properly treated, people with ankylosing spondylitis may lead fairly normal lives. Under ideal circumstances, a team approach to treat spondylitis is recommended. Members of the treatment team typically include the patient, doctor, physical therapist, and occupational therapist. In patients with severe deformities, osteotomy and fusion can be done.

- **Physical and occupational therapy.** Early intervention with physical and occupational therapy is important to maintain function and minimize deformity.
- **Exercise.** A program of daily exercise helps reduce stiffness, strengthen the muscles around the joints and prevent or minimize the risk of disability. Deep breathing exercises may help keep the chest cage flexible. Swimming is an excellent form of exercise for people with ankylosing spondylitis.
- **Medications.** Certain drugs help provide relief from pain and stiffness, and allow patients to perform their exercises with minimal discomfort. Nonsteroidal anti-inflammatory drugs (NSAIDs) -- such as ibuprofen, naproxen, and aspirin -- are the most commonly used drugs for spondylitis treatment. In moderate to severe cases, other drugs may be added to the treatment regimen. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (Rheumatrex), can be used when NSAIDs alone are not enough to reduce the inflammation, stiffness, and pain. In addition, relatively new drugs called biologics adalimumab (Humira), adalimumab-atto (Amjevita), a biosimilar to Humira, certolizumab pegol (Cimzia), etanercept (Enbrel), etanercept-szzs (Erelzi), a biosimilar to Enbrel, golimumab (Simponi Aria, Simponi), infliximab (Remicade), and infliximab-dyyb (Inflectra), a biosimilar to Remicade, and secukinimab (Cosentyx)-- have been FDA-approved for treating ankylosing spondylitis. Also, the antidepressant Cymbalta has been approved for chronic back pain as well. Steroid injections into the joint or tendon may be helpful in some cases.
- **Surgery.** Artificial joint replacement surgery may be a treatment option for some people with advanced joint disease affecting the hips or knees.

AIM AND OBJECTIVE

Aim of present study is investigated formulation development and evaluate of etoricoxib orally disintegration tablet by using ion exchange resin technique, in different concentrations to enhance the disintegration profile. Research is focused to improve the therapeutic efficacy of the one of the most promising drug meant for the treatment of rheumatoid arthritis, osteoarthritis and gout.

Objective:

- To formulate development and evaluate solid unit dosage form of etoricoxib orally disintegrating tablet.
- To perform the drug – excipient compatibility studies as per ICH guidelines
- To study the disintegration time, taste masking of ion exchange resin complexation technique
- To study the rate and mechanism of dissolution process.
- To study the stability of the formulated drug.

PLAN OF WORK

The following experiment protocol was designed to prepare the predetermined aim of the present study.

Preformulation study for AIP:

- AIP characterization (flow properties, particle size distribution)
- Solubility studies
- Drug-excipient compatibility studies (FTIR)
- UV method development

Formulation and evaluation of ODT:

Preformulation study:

- Angle of repose
- Bulk density
- Tapped density
- Compressibility
- Hausner ratio

Postformulation study:

- Weight variation
- Hardness
- Thickness
- Friability
- Disintegration
- Dissolution

To carry out the Accelerated stability studies of the final formulated product as per ICH guidelines.

MATERIAL METHOD

Table no. 18 materials:

S no.	Excipients	Manufacture
1	Etoricoxib	Acumen pharmaceutical
2	Polacrilin potassium	FMC biopolymer Hyderabad
3	Tartaric acid	Lubrizol mumbai
4	Pearlitol flash	Avantor hyderabad
5	Crospovidone	Lubrizol mumbai
6	Croscarmellose sodium	IMc pharmaceutical
7	Sucralose	Lubrizol mumbai
8	Neotame	Avantor hyderabad
9	Orange flaver	IMc pharmaceutical
10	Peperment flaver	Avantor hyderabad
11	Sunset yellow	Lubrizol Mumbai
12	Talc	Avantor Hyderabad
13	Magnesium stearate	IMc pharmaceutical

LIST OF EQUIPMENTS

Table no .19 list of equipment's:

S NO.	INSTRUMENTATION	MANUFACTURE/SUPPLIERS
1	Precision balance	Afcoset, Mumbai
2	Vernier	Labindia, Mumbai
3	Friabilator	Pharmatest, Mumbai
4	Hardness tester	Strong cob, Monsanto, Mumbai
5	Dissolution apparatus	Labindia, Mumbai
6	Tablet compression machine (single station)	Cadmach machinery co.., ahemdabad
7	Uv spectroscopy	Shimadzu, japan,
8	Hot air oven	Biotech india
9	FTIR spectroscopy	Shimadzu, japan,

Preformulation studies:

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rationale development of dosage forms. Pre-formulation studies yield necessary knowledge to develop suitable formulation. It gives information needed to define the nature of drug substance and provide a dosage form. Hence, the following pre-formulation studies were performed for the obtained sample of drug.

- Organoleptic evaluation
- Drug – excipients compatibility
- FTIR drug – excipients compatibility
- Particle size distribution
- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner's ratio
- Solubility studies
- Loss on drying
- UV method development for estimation of drug resin complex formation
- UV method development for estimation of drug

Post formulation study:

- Weight variation test
- Hardness
- Thickness
- Friability
- Disintegration time
- Assay
- Dissolution study

Organoleptic evaluation:

The organoleptic property of

- Color
- Taste
- Odor
- Flavor

Drug – excipients compatibility:

Fourier transform infrared spectroscopy:

FT-IR stands for Fourier transform infrared, the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiations is absorbed by the sample and some of it is passed through (transmitted). The resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the sample. Like a fingerprint no two unique molecular structures produce the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis. FT-IR samples were mixed with KBr in ratio 1:3 and pressed into pellets. Pellets were analyzed at wavelength range 4000-450cm^{-1} with resolution of as 4cm^{-1} and number of scans

Drug – excipients physical compatibility:

The study of physical appearance,

- Color
- Shape
- Size

Particle size determination:

Table no. 20

S no.	Sieve number	Opening size (mm)
1	4	4.750
2	6	3.350
3	8	2.360
4	12	1.680
5	16	1.180
6	20	0.850
7	30	0.600
8	40	0.425
9	50	0.300
10	60	0.250

Dry sieving method

An accurately weighed quantity of test specimen was placed on the top (coarsest) sieve, and lid was replaced. The nest of sieves was agitated for 5 minutes. Then each sieve was carefully removed from the nest without loss of material. Each sieve was reweighed, and the weight of material on each sieve was determined. The weight of material in the collecting pan was also determined in similar manner. The nest of sieves were reassembled and agitated for 5mins. Each sieve was removed and weighed, as previously described. Upon completion of the analysis, the weights of material were reconciled. Total losses must not exceed 5% of the weight of original test specimen.

Table no. 21 Classification of powder by fineness:

S no.	Classification of powder	Sieve opening (µm)
1	Very coarse	>1000
2	Coarse	355-1000
3	Moderately fine	180-355
4	Fine	125-180
5	Very fine	90-125

Angle of repose:

The angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density surface area,

and coefficient of friction of the material. Material with a low angle of repose forms flatter piles than material with a high angle of repose. In other words, the angle of repose is the angle a pole forms with the ground.

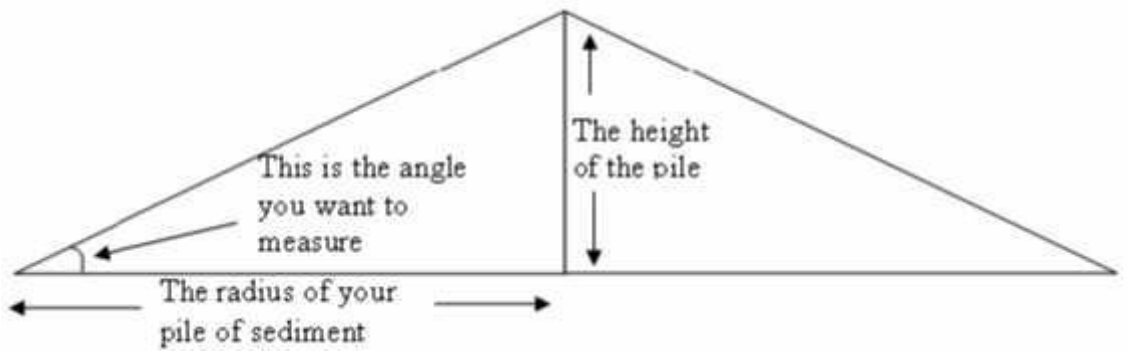


Figure.28 angle of repose

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = tan^{-1}\left(\frac{h}{r}\right)$$

h = height of pile,

r = radius of pile, and

Θ = angle of repose

Table no. 22 flow property of angle of repose:

S no.	Flo property	Angle of repose
1	Excellent	25-30
2	Good	31-35
3	Fair	36-40
4	Passable	41-45
5	Poor	46-55

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

$Bulk\ density = M/V_0$

Where M= mass of the powder;

V_0=bulk volume of the powder.

Limits: It has been stated that the bulk density values having less than 1.2 g/cm^3 indicates good packing and values greater than 1.5 g/cm^3 indicates poor packing.

Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed.

$Tapped\ density = M/V_r$

Where

M = mass of the powder,

V_r = final tapping volume of the powder.

Compressibility index and Hausner ratio:

The compressibility index and Hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

$Compressibility\ index = 100\ x\ tapped\ density/bulk\ density$

$Hausner\ ratio = tapped\ density/bulk\ density$

Table no.23

Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio Acceptance criteria of flow properties:

S no.	Flow property	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Possible	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Practically poor	>66	>38	>1.6

Loss on drying:

The Loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (1.5g) was determined by using electronic LOD (helium lamp) apparatus at 105°C.

Weight variation test:

Twenty tablets were selected randomly and the average weight was determined using an electronic balance (P/PI-203MDS model, Denver instruments). Tablets were weighed individually and compared with the average weight.

Hardness test:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in Kg/cm2.

Thickness test:

Ten tablets were selected randomly and thickness was assessed using a Vernier caliper/screw gauge.

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport.

Friability of the tablets was determined using Roche friabilitor at 25 rpm/min for 4 min. The device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Twenty tablets were weighed and loss in weight (%) was calculated. The friability (F) is given by the formula,

$$\% \text{ Friability} = [(W1-W2)100]/W1$$

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test

Assay:

Standard stock solution:

30mg of drug resin was taken and added to respective media in a 200 ml volumetric flask and volume was made up to 200 ml, resulting in a standard stock solution of 150mcg/ml.

Working stock solution:

From the above standard stock solution 1ml was taken and added to the respective buffer media in 25ml volumetric flask and the volume was made up to 25ml. Two working stocks were prepared and that they can be used for preparation of samples.

Determination of absorption maxima:

6µg/ml solutions were taken to determine absorption maxima. Initially blank buffer solution is kept and scanned in the region of 200-400 nm. Then sample was for analysis and scanned at the same region. The absorption maximum was found to be, Hence all further analysis was carried out at 263nm in pH7.0 phosphate buffer.

UV method development for estimation of drug:

Preparation of buffer media:

7.0pH Phosphate buffer:

0.38g of monobasic sodium phosphate and 10g of sodium laryl sulphate is taken in 1000ml of water and adjusted to P^H 7.0 with sodium hydroxide.

Standard stock solution:

30mg of etoricoxib was taken and added to respective media in a 200 ml volumetric flask and volume was made up to 200 ml, resulting in a standard stock solution of 100mcg/ml.

Working stock solution:

From the above standard stock solution 1ml was taken and added to the respective buffer media in 25ml volumetric flask and the volume was made up to 25ml. Two working stocks were prepared and that they can be used for preparation of samples.

Determination of absorption maxima:

6µg/ml solutions were taken to determine absorption maxima. Initially blank buffer solution is kept and scanned in the region of 200-400 nm. Then sample was for analysis and scanned at the same region. The absorption maximum was found to be, Hence all further analysis was carried out at 263nm in pH7.0 phosphate buffer.

Disintegration study:

The disintegration test determines whether dosage forms such as tablets, capsules, suppositories disintegrate with in a prescribed time when placed in a liquid medium under the prescribed experimental conditions. Disintegration is defined as the state in which no residue of the unit under test remains on the screen of the apparatus or if a residue remains it consists of fragments of disintegrated parts of tablet component part such as insoluble coating of tablets. Disintegrants are agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule "slugs'' into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. Disintegrants are an essential component to tablet formulations. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrant action.

There are three methods of incorporating disintegrating agents into the tablet:

A. Internal Addition (Intragranular)

B. External Addition (Extragranular)

C. Partly Internal and External.

Dissolution test:

The dissolution rate of etoricoxib tablets prepared was studied in phosphate buffer of pH 7.0 using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature 37±0.5 $^{\circ}$C was maintained throughout the study. One tablet containing 60 mg of etoricoxib was used in each test. Samples of dissolution media (5ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed at 289 nm for etoricoxib. The samples of dissolution fluid withdrawn at each time were replaced with fresh fluid. The dissolution experiments were replicated three times each (n=3).

FORMULATION DEVELOPMENT

Table no. 24:

S NO.	INGREDIENT	CATEGORY
1	Etoricoxib	Pharmaceutical active ingredient

Table no.25:

S.NO.	INGREDIENT	CATEGORY
1	Indion 294	Ion Exchange Resin
2	Kyron T314	Ion Exchange Resin

Table no. 26 Excipients list:

S No.	Excipients	Category
1	Tartaric Acid	Buffering Agent
2	Pearlital Flash	Diluvant
3	Croscarmellose Sodium	Disintegrating Agent
3	Crospovidone	Disintegrating Agent
5	Sucralose	Sweetening Agent
6	Neotame	Sweetening Agent
7	Sunset Yellow	Coloring Agent
8	Orange Flavor	Flavoring Agent
9	Peppermint Flavor	Flavoring Agent
10	Aerosil	Glident
11	Talc	Lubricant
12	Magnesium stearate	Lubricant

Table no. 27 Formation of drug resin complex

S NO.	Ingredients	Resin complex code (mg/T)					
1	Etoricoxib	DRC1	DRC2	DRC3	DRC4	DRC5	DRC6
		60.00	60.00	60.00	60.00	60.00	60.00
2	Indion 294	60.00	60.00	60.00	120.00	180.00	-
3	Tartaric acid	-	25.00	50.00	50.00	50.00	50.00
4	Kyron t 314	-	-	-	-	-	180.00
5	Purified water	q.s	q.s	q.s	q.s	q.s	q.s

Preparation of complex:

The preparation is done by ion exchange resin complex technique. The drug and the resin (indion294) are taken in the ratio of 1:3.

Resin activation process:

The resin activation process is nothing but the soaking of resin in water. The resin soaked for 45 minutes in water and the resin swells.

P^H adjustment:

The P^H of activated resin is adjusted to 3-4 by using tartaric acid. The tartaric acid used as the buffering agent.

Stirring process:

The P^H adjusted resin and drug are mixed in a same beaker with mechanical stirrer for 8 hours in 1000 rpm. After completion of stirring (8 hours). Then the drug resin complex is set aside stably for 12 hours. Two layers get separated. The upper layer (supernatant fluid) is water and the lower layer (suspansoide) is drug resin complex.

Drying of complex:

To collect the suspansoide it is dried to 50-60^{0}C for 4-5 hours in a hot air oven.

Finishing process:

After drying the drug resin complex it is checked for LOD. Then the drug resin complex was collected.

Table no.28 Dispersion improvement/ taste formulation

S NO.	Ingredient	Dispersion improvement code (mg/t)			Taste improvement code (mg/t)		
		EDI-1	EDI-2	EDI-3	ETI-1	ETI-2	ETI-3
1	DRC-5	290.00	290.00	290.00	290.00	290.00	290.00
2	Croscarmellose sodium	20.00	-	20.00	20.00	20.00	20.00
3	Crospovidone	-	20.00	20.00	20.00	20.00	20.00
4	Pearlital flash	78.20	78.20	58.20	52.20	52.20	46.20
5	Sucralose	-	-	-	6.00	-	6.00
6	Neotame	-	-	-	-	6.00	6.00
7	Sunset yellow	1	1	1	1	1	1
8	Orange flavor	0.50	0.50	0.50	0.50	0.50	0.50
9	Peppermint flavor	0.30	0.30	0.30	0.30	0.30	0.30
10	Aerosil	4.00	4.00	4.00	4.00	4.00	4.00
11	Talc	2.00	2.00	2.00	2.00	2.00	2.00
12	Magnesium Stearate	4.00	4.00	4.00	4.00	4.00	4.00
	Total	400.00	400.00	400.00	400.00	400.00	400.00

Preparation of orally disintegration tablet:

To collect the drug + resin complex and excipients.

Sieving process:

The drug resin complex and excipients are passed through the sieve numbers 20, and 40 respectively.

The granules are collected. The drug resin complex is one more time checked for LOD content level.

Blending process:

The granules of drug resin complex and excipients are collected. And the granules are blended.

Tablet compression process:

The blended granules were involved in direct compression process. The granules are converted to the oral disintegration tablet.

RESULT AND DISCUSSION

Organoleptic properties of etoricoxib:

Table no. 30 Properties of Etoricoxib:

S NO.	Properties	Observation
1	Description	Etoricoxib is a yellow crystalline powder
2	Color	Yellow ion oxide

Drug-excipient compatibility:

Drug-excipient compatibility is tabulated as follows: Physical observation of drug-excipient compatibility study

Table no. 31 Drug-Excipients compatibility:

S NO.	Physical mixture	Observation 3 month	
		25^0C/60%RH	40^0C/60%RH
1	Drug	Yellow color	Yellow color
2	Polacrilin potassium	White crystal	White crystal
3	Pearlitol flash	White crystal	White crystal
4	Crospovidone	White powder	White powder
5	Croscarmellose sodium	White powder	White powder
6	Sucralose	White crystal	White crystal
7	Neotame	White crystal	White crystal
8	Orange flavor	Brownish	Brownish
9	Peppermint flavor	Brownish	Brownish
10	Talc	White powder	White powder
11	Magnesium stearate	White powder	White powder

Fourier Transform-Infrared spectroscopy:

Drug excipient compatibility was analyzed using FT-IR. FT-IR was done using Perkin-Elmer spectrum. All the samples were mixed properly with KBr in 1:3 ratios and were made into pellets. Those pellets were analyzed. Each KBr disc was scanned over a wave number region of 4000-400 cm-1 using FT-IR Spectrophotometer.

FTIR Spectrum of etoricoxib pure drug:

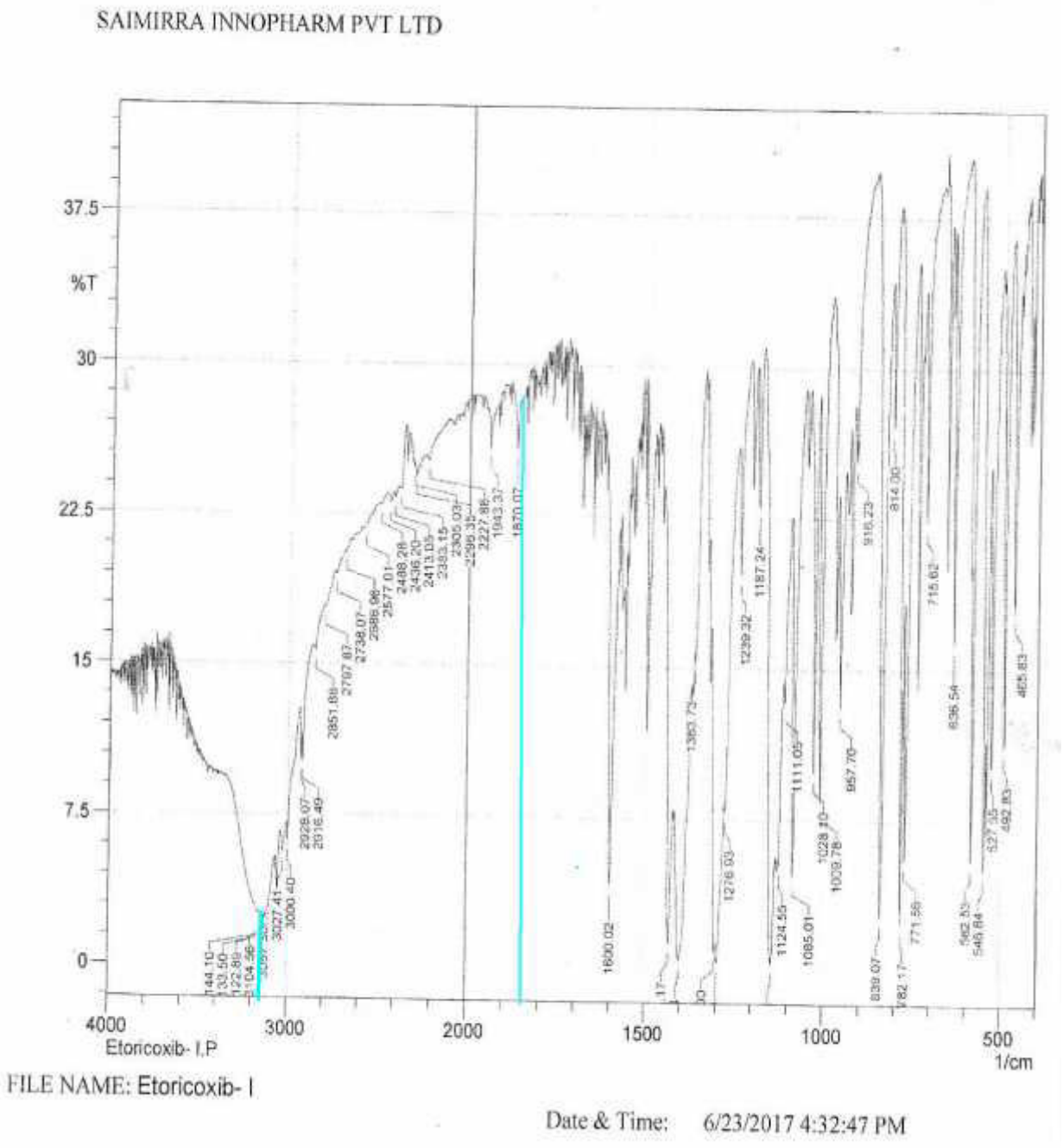


Figure 29 Etoricoxib pure drug

FTIR Spectrum of etoricoxib placebo: (WITH OUT API)

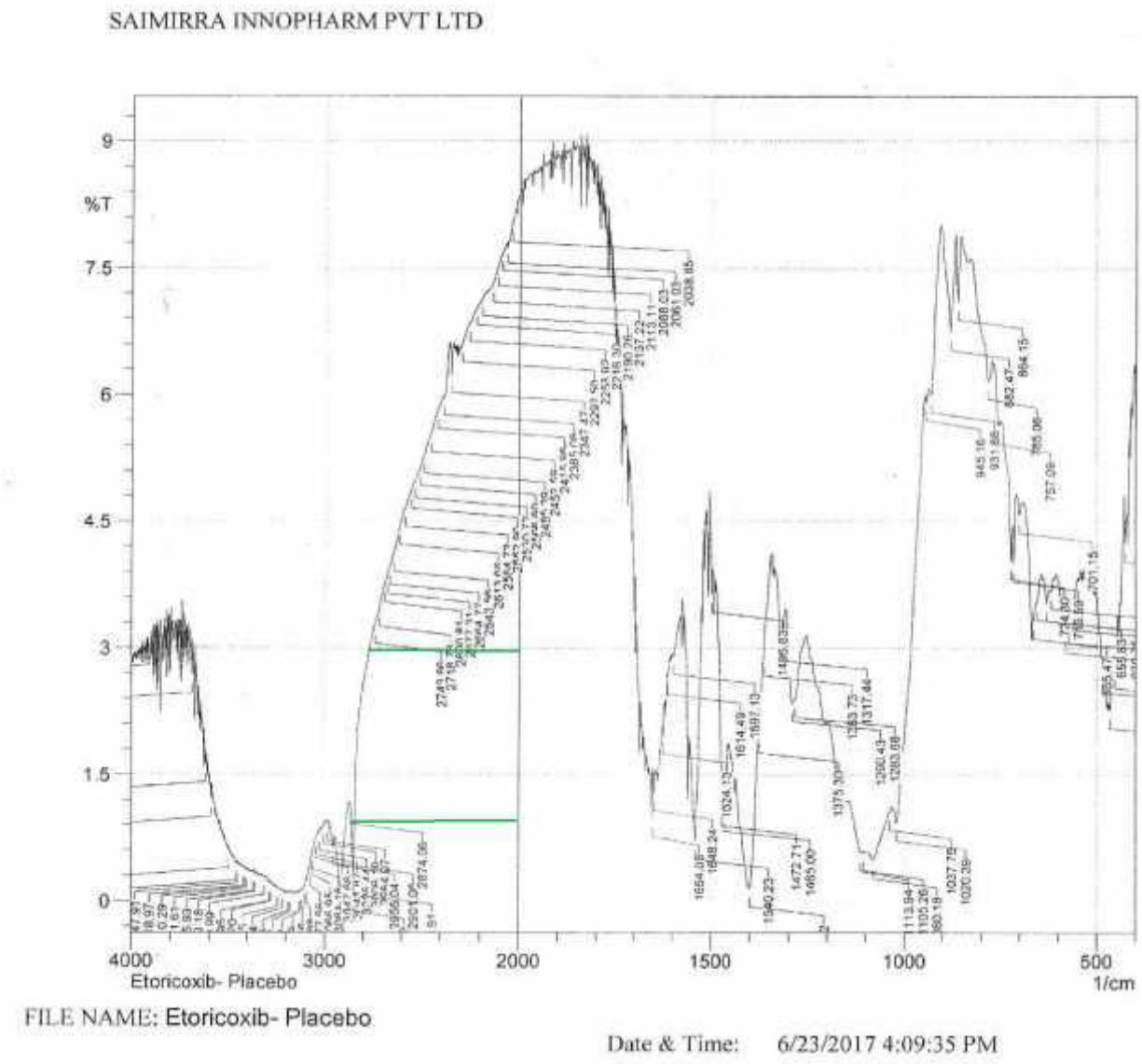


Figure 30 Etoricoxib placebo (without drug)

FTIR Spectrum of etoricoxib blend:

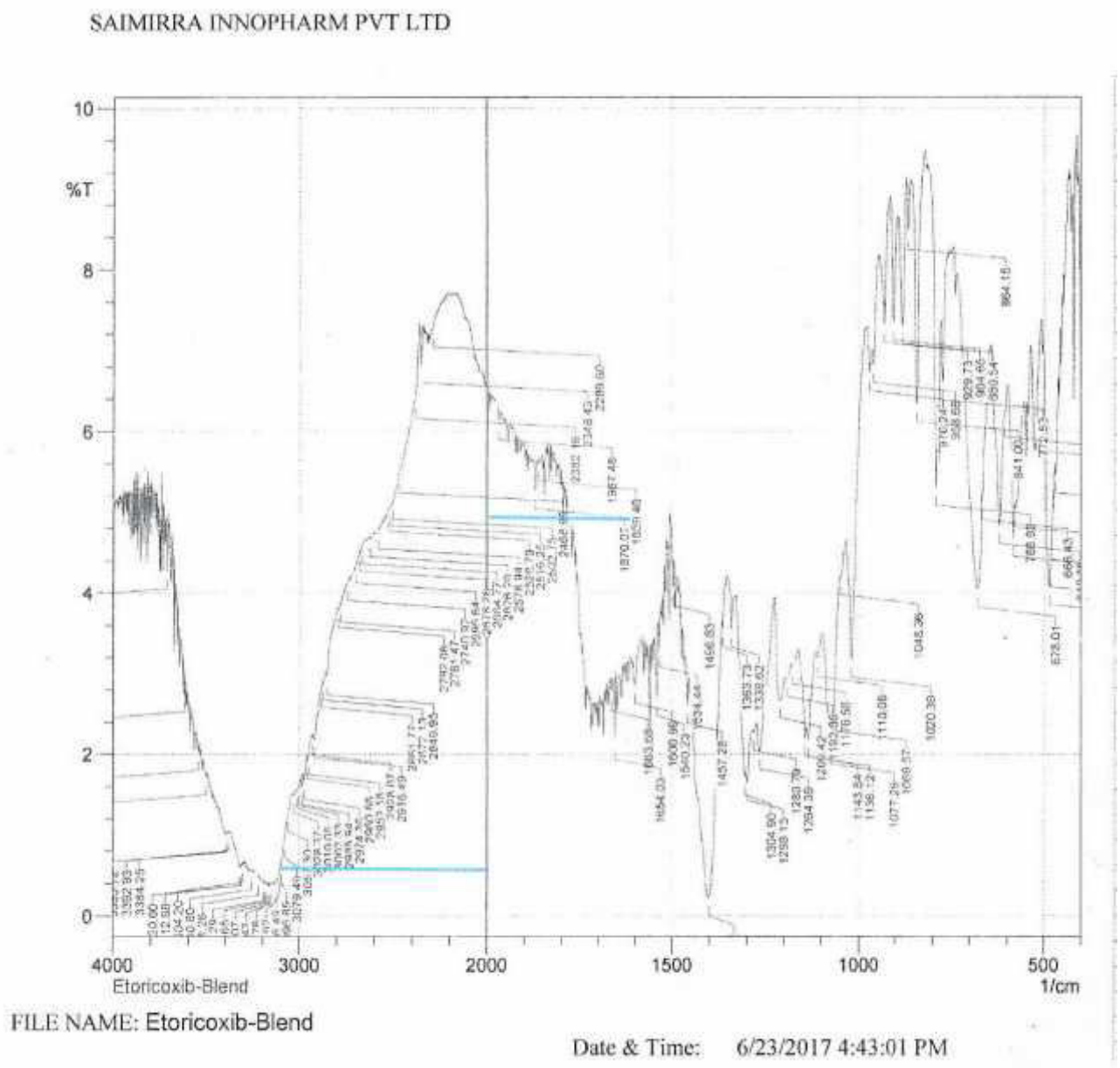


Figure 31 Etoricoxib blend

FT-IR on the selected formulation prepared with different polymer and excipients combination. The spectrum peak point of the formulation were similar with that of pure etoricoxib, it clearly indicates that there are no polymer interaction.

Particle size determination:

The particle size was determined by using sieving method.

Table no.32

S NO.	Ingredient	Sieve number	Particle size
1	Etoricoxib	20	0.850
2	Excipients	40	0.425

FLOW PROPERTIES OF ETORICOXIB:

Table no.33

S.NO	**Angle of Repose Mean ± SEM**	**Bulk density Mean ± SEM**	**Tapped density Mean ± SEM**	**Carr"s Index Mean ± SEM**	**Hausner's Ratio (H) Mean ± SEM**
1	22.62	0.64	0.63	14.51	1.22
2	22.91	0.60	0.65	14.41	1.24
3	23.95	0.63	0.67	14.74	1.26
	23.16 ± 0.403	0.62 ± 0.01	0.66 ± 0.011	14.55 ± 0.097	1.24±0.01

All values are expressed as mean ± SEM for three determinations

Evaluation flow properties of blend:

Table no. 34 Evaluation parameter:

Formulation code	Evaluation parameter					
	Angle of repose	**Bulk density (g/cm^3)**	**Tapped density (g/cm^3)**	**Compressibility Index (%)**	**Hausners ratio**	**Flowability**
EDI 1	25.15	0.571	0.699	14.64	1.17	Excellent
EDI 2	26.35	0.586	0.684	14.32	1.16	Excellent
EDI 3	24.21	0.579	0.674	14.09	1.20	Fair
ETI 1	28.65	0.568	0.667	14.84	1.17	Excellent
ETI 2	23.95	0.578	0.678	14.74	1.18	Excellent
ETI 3	27.84	0.588	0.688	17.53	1.23	Fair

Inference:

Compressibility index**,** angle of repose, bulk density, tapped density and hausner ratio of trial batches were computed and found that all blends possess good flow properties and hence suitable for direct compression of blends into tablets.

Saturation solubility:

. **Table no. 35**

S NO.	Medium	Solubility
1	Methanol	Soluble
2	Water	Insoluble
3	7.0 phosphate buffer	Soluble

Result and discussion of complex formation:

Table no. 36 Result and discussion of complex formation:

S.NO	Formulation	Observation/P^H	Drug complexation %	Taste
1	DRC-1 120mg=60mg	P^H-9.2, Separation layer. No complex formation	-	-
2	DRC-2 145mg=60mg	P^H-5.2, no separation complex is formed	85.6%	-
3	DRC-3 170mg=60mg	P^H-3.5, no separation. Complex is formed	99.2%	Slightly bitter
4	DRC-4 230mg=60mg	P^H-3.68, no separation. Complex is formed	99.38%	Slightly bitter
5	DRC-5 290mg=60mg	P^H-3.85, no separation. Complex is formed	99.82%	Bland taste
6	DRC-6 290mg=60mg	P^H-3.56, no separation. Complex is formed	78.87%	Bitter

CALIBRATION CURVE:

Table No. 37 Calibration curve:

S NO.	Concentration (µg)	Absorbance
1	0	0
2	5	0.218
3	10	0.406
4	15	0.624
5	20	0.848

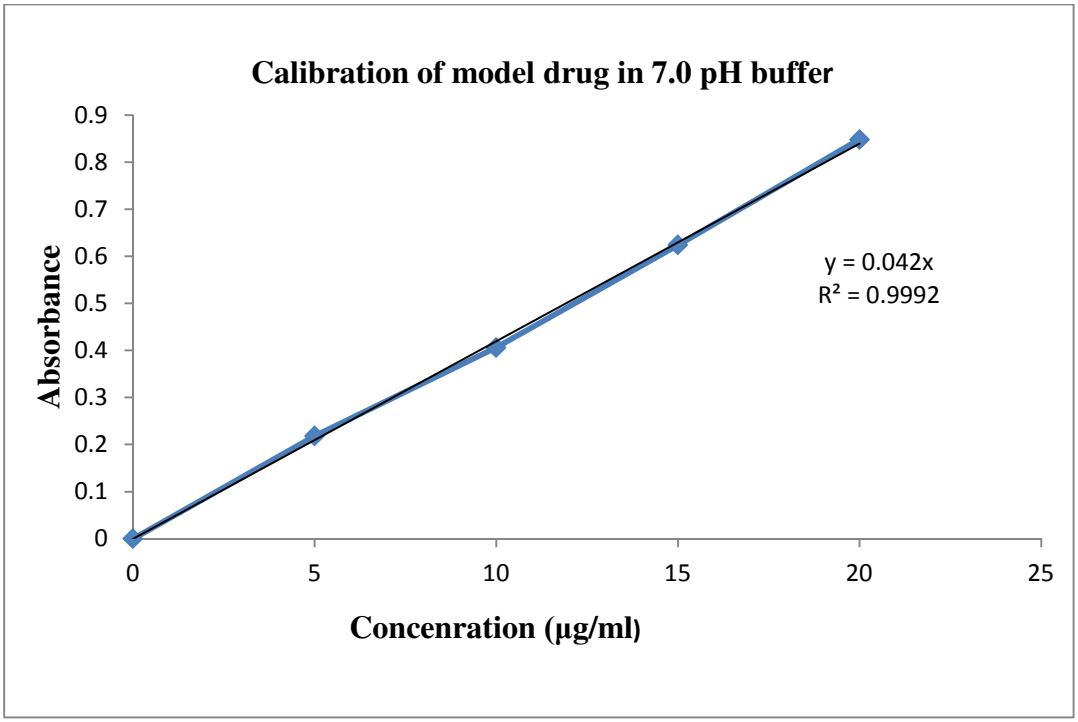


Figure No. 32 Calibration Curve

The ƛ max of etoricoxib was found to be 240 nm. The linear equation was y = 0.042 x (x=concentration µg/ml). Different standard concentration and their absorbance were shown in the table. Regression value of calibration curve is 0.999. A graph of Absorbance Vs Concentration was found to be linear indicating its compliance with beer's law.

Evaluation of compression parameters:

Weight variation Test:

Table No. 38 Weight variation Test:

S NO.	Formulation	Weight variation (mg) (Mean±SEM)
1	EDI 1	403±0.96
2	EDI 2	402±0.71
3	EDI 3	403±0.32
4	ETI 1	404±0.55
5	ETI 2	401±0.39
6	ETI 3	402±0.62

All values are expressed as mean ± SEM for twenty determinations

Thickness:

Table no. 39 Thickness test:

S NO.	Formulation	Average weight of tablet (mg)	Average thickness (mm) Mean ± SEM
1	EDI 1	402	3.5 ± 0.09
2	EDI 2	401	3.7 ± 0.09
3	EDI 3	403	3.8 ± 0.09
4	ETI 1	403	3.9 ± 0.09
5	ETI 2	402	3.8 ± 0.09
6	ETI 3	402	3.9 ± 0.09

All values are expressed as mean ± SEM for three determinations

Hardness:

Table No. 40 Hardness:

S NO.	Formulation	Average hardness (kg/cm^2)
1	EDI 1	4.3
2	EDI 2	4.1
3	EDI 3	4.2
4	ETI 1	4.3
5	ETI 2	4.5
6	ETI 3	4.4

All values are expressed as mean ± SEM for three determinations

Friability:

Table No. 41 friability:

S NO.	Formulation	Friability
1	EDI 1	0.5%
2	EDI 2	0.7%
3	EDI 3	0.6%
4	ETI 1	0.8%
5	ETI 2	0.6%
6	ETI 3	0.9%

All values are expressed as mean ± SEM for three determinations

Drug content:

Table no. 42 Drug content:

S NO.	Formulation	Drug content uniformity (%)
1	EDI 1	91.20%
2	EDI 2	91.67%
3	EDI 3	93.80%
4	ETI 1	94.40%
5	ETI 2	96.23%
6	ETI 3	95.33%

Disintegration test:

Table no.43 Disintegration test:

S NO.	Disintegration test (sec) EDI-1	Disintegration test (sec) EDI-2	Disintegration test (sec) EDI-3	Disintegration test (sec) ETI-1	Disintegration test (sec) ETI-2	Disintegration test (sec) ETI-3
1	52	53	48	44	39	45
2	55	53	45	43	39	48
3	52	55	47	45	38	47
4	58	54	50	44	35	50
	52 ± 0.05	54± 0.03	48 ± 0.05	44 ± 0.02	37 ± 0.03	47 ± 0.03

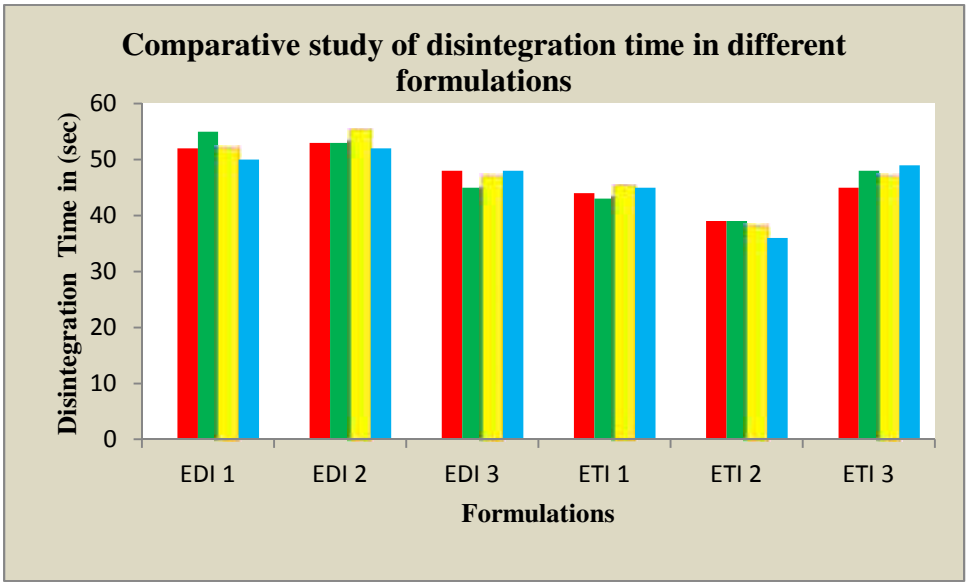


Figure 33 Comparative study of disintegration time in different formulations

Table no.44 Disintegration time:

S NO.	Formulation	Disintegration time (sec)
1	EDI 1	58
2	EDI 2	54
3	EDI 3	50
4	ETI 1	44
5	ETI 2	35
6	ETI 3	47

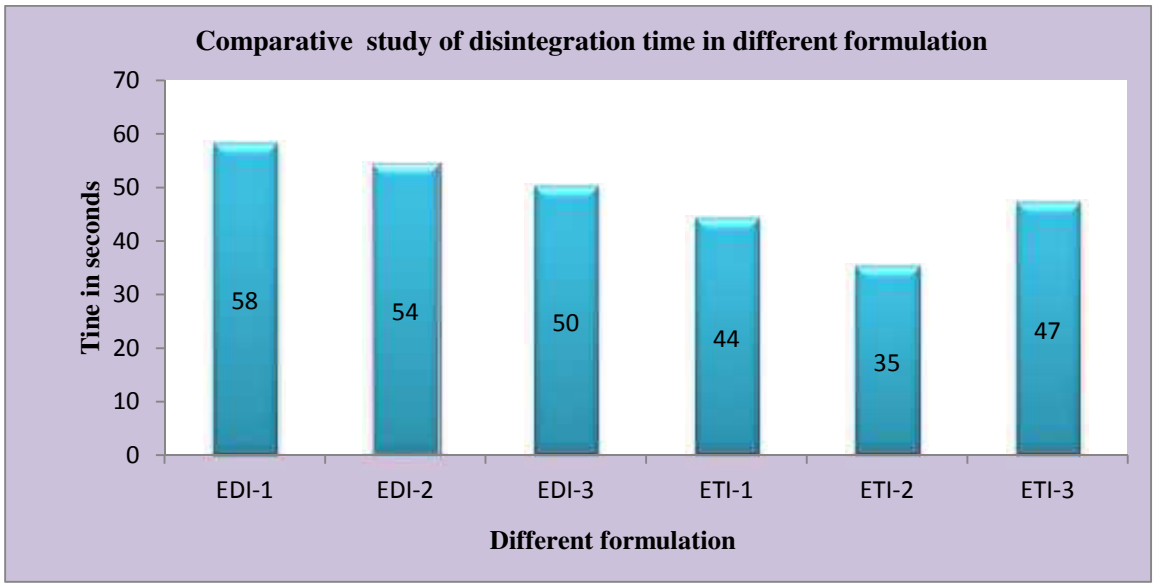


Figure no.34 Comparative study of different disintegrates

From the above data it was found that when crospovidone and croscarmellose sodium was used in the formulation (ETI 2), the disintegration time found to be limited value of orally disintegration tablet.

IN VITRO DISSOLUTION:

Dissolution profile of formulation:

The dissolution of formulation EDI 1, EDI 2, EDI 3, ETI 1, ETI 2, ETI 3 was carried out and the % **drug release**

Table no. 45 Dissolution profile of formulation of ODT tablet

Time	Dissolution test (con/time) EDI-1 %	Dissolution test (con/time) EDI-2 %	Dissolution test (con/time) EDI-3 %	Dissolution test (con/time) ETI-1 %	Dissolution test (con/time) ETI-2 %	Dissolution test (con/time) ETI-3 %
0	0	0	0	0	0	0
10	28.25	28.25	30.21	31.41	43.25	29.33
20	65.33	45.33	58.99	55.33	64.99	57.22
30	84.24	76.88	78.96	79.25	82.99	76.33
45	87.23	85.25	92.47	89.45	95.89	94.66

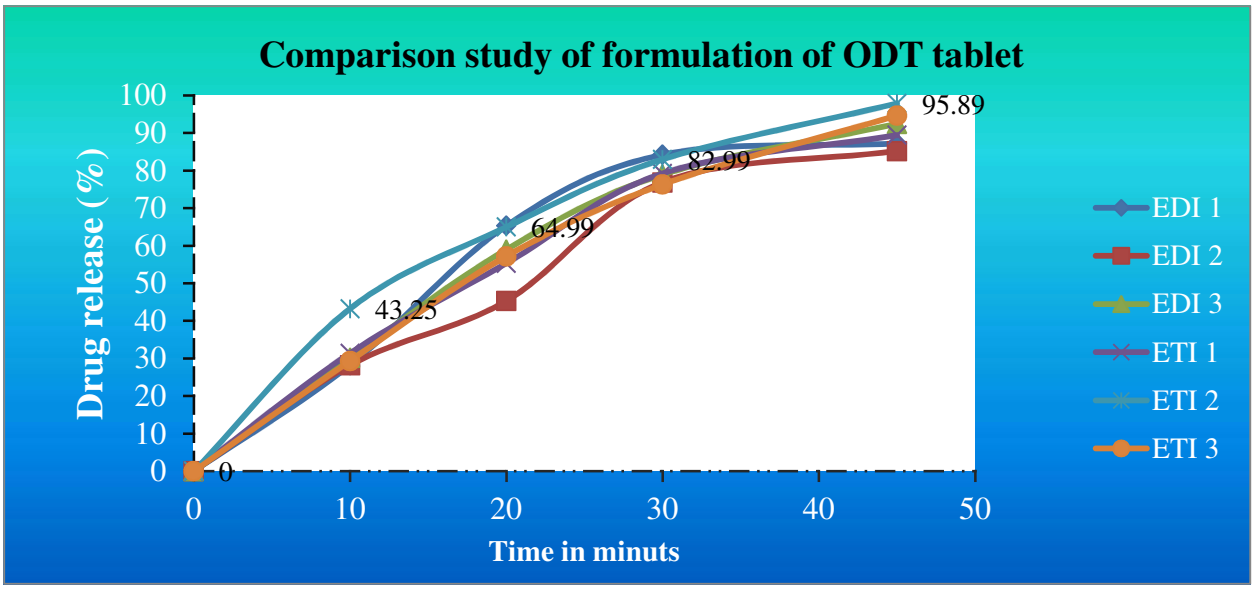


Figure no. 35 Comparative study of formulations:

From the above data it was found that when crospovidone and croscarmellose sodium was used in the formulation (ETI 2), the %drug release was found to be 95.89% at 45 mins time.

Comparison study of formulation tablet and marketed tablet:

Table no. 46 Comparison and study of formulation tablet marketed tablet

Time	Dissolution test (conc/time) EDI 1	Dissolution test (conc/time) EDI 2	Dissolution test (conc/time) EDI 3	Dissolution test (conc/time) ETI 1	Dissolution test (conc/time) ETI 2	Dissolution test (conc/time) ETI 3	Dissolution test (conc/time) Marketed sample
0	0	0	0	0	0	0	0
10	28.25	27.78	30.21	31.41	43.25	29.33	25.22
20	65.33	45.33	58.99	55.33	64.99	57.22	58.99
30	84.24	76.88	78.96	79.25	82.99	76.33	82.99
45	87.23	85.25	92.47	89.45	95.89	90.66	95.55

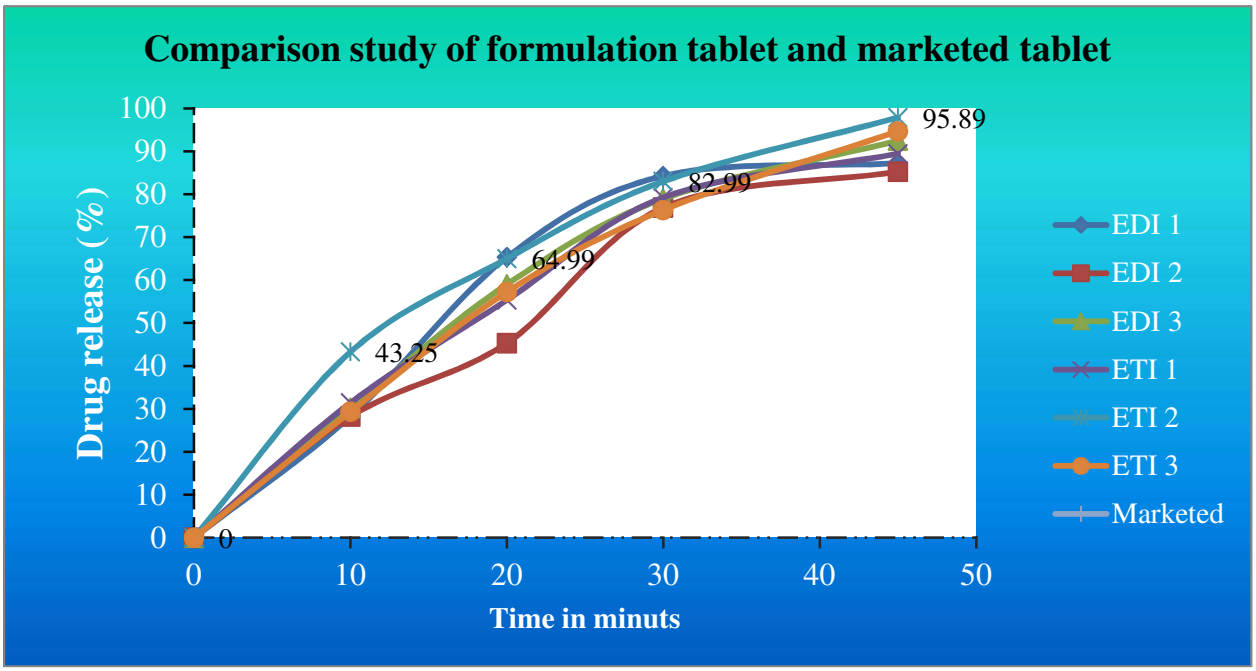


Figure no. 36 formulation-marketed tablet

It is evident from the all formulations exhibit rapid and complete dissolution profile. Formulation (ETI 2), exhibits the better dissolution profile than compared with marketed ODT formulations.

Comparison study of marketed sample and ETI 2:

Table no. 47 Comparison study of marketed sample and ETI 2:

Time	ETI 2 (drug concentration)	Marketed tablet (drug concentration)
0	0	0
10	43.25	25.22
20	64.99	58.99
30	82.99	82.99
45	95.89	95.55

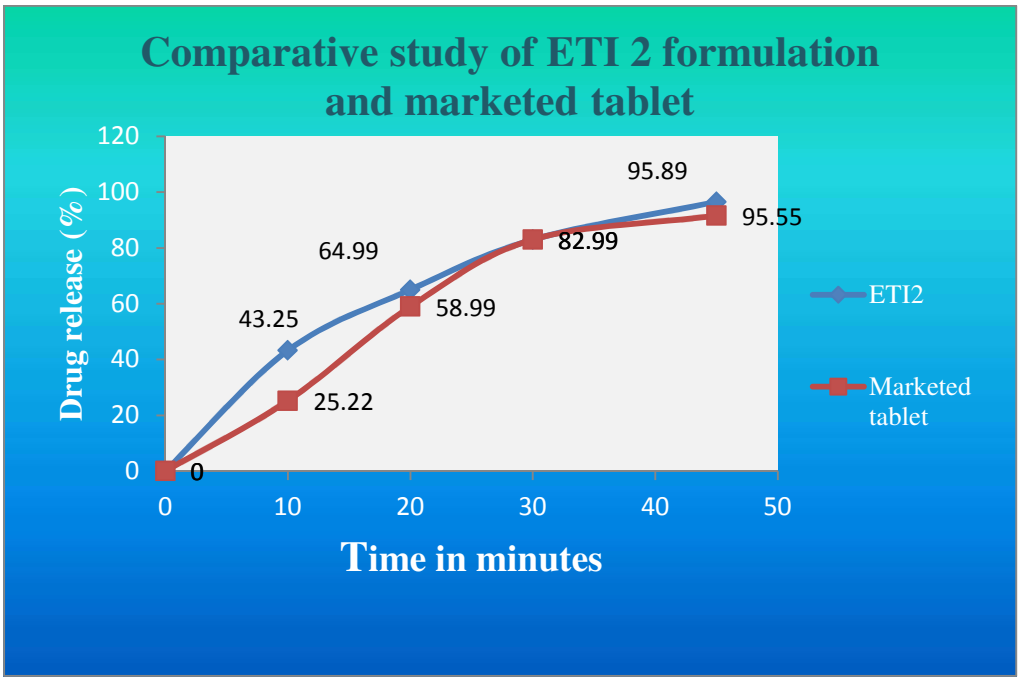


Figure No. 37 ETI 2-marketed tablet

Formulation (ETI 2), exhibits the better dissolution profile than compared with marketed ODT formulations.

STABILITY STUDIES ON SELECTED ODT TABLETS FORMULATION

Quality guidelines known as ICH guidelines have established a series of guidelines acceptable to multiple countries for the drug approval process. (ICH Guidelines) It is a normal practice to study the stability of pharmaceutical preparations at accelerated conditions of temperature and humidity, the experimental findings which can be transformed into reliable shelf life or expiry date by adopting certain assumptions or criterions (Cannorset al.1979). In comparison to conventional preparations Pharmaceutical product represents number of unique problems when quality and stability are considered. To ensure proper reproducibility, proper control is essential an important part of quality control is to ensure the chemical stability of final product during storage product. Present study is an attempt to study accelerated stability of ODT tablets, these have been prepared using time tested pharmaceutical ingredient in optimum concentration which includes etoricoxip ODT formulation.

METHODS

The present work on "Accelerated Stability study of Herbal Capsules" was undertaken to standardize and study the stability profile of ODT tablets formulation. The study was done at accelerated temperature and humidity conditions, i.e. accelerated stability study taking ICH guidelines as reference. The ten tablets were randomly collected. Enough blisters in duplex were kept in humidity chamber at 40^0 $\pm 2^0$ c and 70 ± 5% RH humidity. Required blisters were withdrawn after one, two, three and six month in triplicate for analysis. The main ingredient of ODT formulation initial sample 1, 2, 3 and 6 month of storage at accelerated conditions of temperature and humidity. For evaluation different parameters were taken that were organoleptic evaluation, identification tests, Average weight test, disintegration test, dissolution test. Samples were tested at the time of their release of batch and after 1st, 2nd, 3rd and 6th month of storage.

Table No.29 Results of different parameters used for Accelerated Stability study data of selected ODT formulations subjected to study as per ICH guidelines (6month at 40°C ± 2°C and 75%RH ± 5% RH). At predetermined time intervals of 1, 2, 3 and 6 month.

Days	Formulation	Colour and Odour	pH	Wight variation test	Friability test	Hardness test	Thickness test	Disintegration test (sec)	Assay	Solubility	Dissolution test
0 Day	EDI -1	Yellow	6.7	404	0.96%	No change	4.4%	39	95.82%	No change	Good
	EDI-2	Yellow	6.4	405	1.01%	No change	4.5%	37	96.21%	No change	Good
	EDI-3	Yellow	6.8	403	1.5%	No change	4.5%	38	97.11%	No change	Good
	ETI-1	Yellow	6.6	402	1.5%	No change	4.3%	40	96.01%	No change	Good
	ETI-2	Yellow	6.3	401	0.9%	No change	4.2%	36	95.22%	No change	Good
	ETI-3	Yellow	6.2	405	1.2%	No change	4.4%	38	94.43%	No change	Good
30 Days	EDI -1	Yellow	6.6	405	1.01%	No change	4.5%	39	95.21%	No change	Good
	EDI-2	Yellow	6.3	403	1.5%	No change	4.2%	39	94.19%	No change	Good
	EDI-3	Yellow	6.7	402	0.9%	No change	4.3%	38	95.15%	No change	Good
	ETI-1	Yellow	6.4	404	1.01%	No change	4.4%	40	96.10%	No change	Good
	ETI-2	Yellow	6.5	405	1.5%	No change	4.5%	39	95.32%	No change	Good
	ETI-3	Yellow	6.4	404		No change	4.3%	39	95.21%	No change	Good
60 Days	EDI -1	Yellow	6.6	404	1.01%	No change	4.4%	37	94.82%	No change	Good
	EDI-2	Yellow	6.0	403	0.9%	No change	4.6%	37	96.37%	No change	Good
	EDI-3	Yellow	6.3	405	1.5%	No change	4.2%	36	96.23%	No change	Good
	ETI-1	Yellow	5.9	401	0.9%	No change	4.1%	38	94.19%	No change	Good
	ETI-2	Yellow	6.7	403	1.01%	No change	4.2%	36	96.23%	No change	Good
	ETI-3	Yellow	6.2	403	0.9%	No change	4.4%	39		No change	Good
90 Days	EDI -1	Yellow	6.5	405	1.5%	No change	4.4%	40	93.21%	No change	Good
	EDI-2	Yellow	5.9	406	0.9%	No change	4.2%	38	94.7%	No change	Good
	EDI-3	Yellow	6.2	405	1.01%	No change	4.1%	38	96.58%	No change	Good
	ETI-1	Yellow	5.9	403	1.5%	No change	4.3%	39	95.19%	No change	Good
	ETI-2	Yellow	6.4	404	0.9%	No change	4.4%	39	94.34%	No change	Good
	ETI-3	Yellow	6.5	403	1.5%	No change	4.1%	38	94.22%	No change	Good

No visible physical and chemical changes observed in any one the product during storage period. ODT tablet formulation conducted Color and Odour, pH, Wight variation test, Friability test, Hardness test, Thickness test, Disintegration test (sec), Assay, Solubility, Dissolution test all the product should be stable in the **Accelerated** storage period of 6 month.

Summary:

The objective of present study is investigated formulation development and evaluated of etoricoxib orally disintegration tablet by using ion exchange resin technique, in different concentrations to enhance the disintegration profile. Etoricoxib is an anti-rheumatoid arthritis drug, which is commonly prescribed for treatment of rheumatoid arthritis, osteoarthritis and gout. It is a slightly soluble in water and it is cox-2 inhibitor. Etoricoxib has long biological half-life (22hrs). In the present study, fast disintegrating tablets of etoricoxib ODT were prepared by ion exchange resin complexation technique for better patient compliance and immediate action in rheumatoid arthritis, and osteoarthritis. The tablets were prepared by using synthetic super-disintegrants such as Cross povidone and croscarmellose sodium.

Preformulation studies:

FTIR showed no major degeneration the drug and excipients combination. The spectrum peak point of the formulation were similar with that of pure etoricoxib, The pre-formulation study carried out that angle of repose, bulk density, tapped density, compressibility, Hausner ratio. The results were clearly shown.

Evaluation of Designed Formulations:

Post formulation studies

Physical characterization of all the lubricated blends were carried out and found to have good flow properties. The tablets prepared with the plain polymer mixture combination were found to have desired limits of hardness and thickness and complies to weight variation and within the official limits of friability. The formulation EDI 1 and EDI 3 was added with disintegrating agent such as crospovidone and croscarmellose sodium respectively. The result was increases the disintegrating time. However the combination of disintegration formulation EDI 2 was to reduce the disintegrating time. Then development study of taste improved process. ETI 1 and ETI 3 each one sweetening agent added like that sucralose and neotame. But taste was not compatible in this formulation. So combination sweeteners formulation ETI 2 is good taste of

this formulation. *In-vitro* drug release for formulations EDI 1, EDI 2, EDI 3, ETI 1, ETI 2, and ETI 3 is carried out. From this the % drug release was found to be better at formulation ETI 2 which is considered as optimized formulation. The drug release for formulation ETI 2 was found to be 95.89% at the end of 45 mins. The prepared tablets were evaluated for Weight variation, Hardness, Friability, Disintegration time, Drug content and in vitro dissolution tests. The results were clearly shown. Accelerated Stability studies were also done for optimized formulation ETI 2 and the results were found satisfactory.

Conclusion:

The results of etoricoxib ODTs evaluation of different batches were done. The FT-IR study shows that there was no interaction between the drug and the polymer. The weight variation of 400mg tablets was found maximum up to ± 1.2 % RSD. Hardness was found to be within 3.0 to 4.0 kg/cm2 which limit friability within 0.7% only. The evaluation results of ETI 2 batches were found to be satisfactory within limit and the **disintegration time (35sec)** was quite good than synthetic mixture combination super disintegrants such as Crospovidone and croscarmellose sodium. As the combination of super disintegratant concentration decrease with same ratio the formulation ETI 2 gave 95.89% drug release at 45 mins time point,. The drug Contents was found to be within limits and all tablets were passing the dispersion test. ODT tablets of etoricoxib of optimized all batch were of satisfactory stability during 6 months of accelerated stability studies.

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